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Effect of hepatitis C virus status on liver enzymes in opioid-dependent pregnant women maintained on opioid-agonist medication

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ABSTRACT

Aim To examine hepatic enzyme test results throughout the course of pregnancy in women maintained on methadone or buprenorphine. **Design** Participants were randomized to either methadone or buprenorphine maintenance. Blood chemistry tests, including liver transaminases and hepatitis C virus (HCV) status, were determined every 4 weeks and once postpartum. As part of a planned secondary analysis, generalized mixed linear models were conducted with aspartate aminotransferase (AST), alanine aminotransferase (ALT) and gamma-glutamyl transferase (GGT) as the dependent variables. **Setting** Six US sites and one European site that provided comprehensive treatment to pregnant opioid-dependent women. **Participants** A total of 175 opioid-dependent pregnant women enrolled in the Maternal Opioid Treatment: Human Experimental Research (MOTHER) study. **Findings** ALT, AST and GGT levels decreased for all subjects across pregnancy trimesters, rising slightly postpartum. HCV-positive subjects exhibited higher transaminases at all time-points compared to HCV-negative subjects, regardless of medication (all *P*s < 0.05) condition. Both HCV-positive and negative buprenorphine-maintained participants exhibited lower GGT levels than those who were methadone-maintained ($P < 0.05$). **Conclusions** Neither methadone nor buprenorphine appear to have adverse hepatic effects in the treatment of pregnant opioid-dependent women.

Keywords Buprenorphine, liver transaminases, methadone, opioids, pregnancy.

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INTRODUCTION

Clinical experience and research have demonstrated that maintenance with an opioid agonist is effective in treating the substance use disorder of opioid dependence. Since the mid-1960s methadone, a synthetic full mu-agonist medication, has been established widely as an effective treatment for opioid dependence. Furthermore, the National Institutes of Health have established methadone as the 'gold standard' for treating opioid-dependent patients during pregnancy [1].

In 2002, buprenorphine was approved by the Food and Drug Administration (FDA) for the treatment of opioid dependence in non-pregnant patients and is considered a safe and effective medication [2–4]. Extensive clinical research in the United States, including large-scale clinical trials involving more than 1,000 patients, has shown that buprenorphine is safe and effective for treating opioid dependence in adults [2,3,5–8]. As a semi-synthetic partial mu-agonist, buprenorphine may offer some potential advantages over methadone as a treatment for opioid dependence. From a pharmacokinetic/pharmacodynamic standpoint, buprenorphine's partial agonistic characteristics demonstrate an improved safety profile, in terms of respiratory depression and other toxic effects of full agonists.

Further, its tight binding to and slow dissociation from opioid receptors permit a long duration of action and are thought to explain the relatively mild withdrawal syndrome noted with buprenorphine discontinuation [9]. Additionally, buprenorphine is available both within and outside (i.e. office-based prescription) opioid treatment programs, making it accessible to a broader range of opioid-dependent individuals.

Long-term methadone therapy has been well tolerated by patients with mild or moderate liver dysfunction and has no known hepatotoxic effects [10]. Treatment with buprenorphine also does not appear to increase liver enzyme levels in opioid-dependent non-pregnant patients without hepatitis [11]. However, concerns regarding potential hepatotoxicity were raised by case reports of acute hepatitis in patients treated for opioid dependence [12], and have led to the recommendation that all buprenorphine-treated patients have tests examining markers of liver function performed at treatment initiation and at intervals thereafter. Petry *et al.* [11] report that some individuals with hepatitis B or C infection who are treated with buprenorphine do experience increases in aspartate aminotransferase (AST) and alanine aminotransferase (ALT). The increases noted were small, and it was unclear if they resulted from buprenorphine treatment or hepatitis infection, as most patients in the sample were hepatitis C virus (HCV)-positive. Berson *et al.* [13] also describe four cases of hepatitis contracted following intravenous buprenorphine misuse in heroin-dependent individuals, but state that this is a 'most uncommon complication even after intravenous misuse, considering the large number of patients (about 65,000) placed on buprenorphine treatment, and the likelihood that a certain number may misuse and inject it intravenously'. Zuin *et al.* [14] also published a case report of one patient, who was HCV-positive, with acute liver and kidney failure on therapeutic doses of buprenorphine. Berson *et al.* [15] further showed in rat hepatic microsomes and mitochondria that the hepatotoxicity of high doses of buprenorphine is related to its impairment of mitochondrial respiration, at concentrations very unlikely to be achieved at clinical sublingual doses.

Overall, the literature has few reports of buprenorphine treatment and hepatic injury or dysfunction in opioid-dependent individuals, but the question of whether buprenorphine may exacerbate existing liver disease remains a topic for study. This is especially salient as the rates for HCV infection reported in the current literature for heroin-using and methadone-maintained populations are as high as 70–90% for injecting drug users [16,17]. Studies focusing on pregnant opioid-dependent women receiving substance abuse treatment report rates of HCV from 11 to 93% [18–22]. While efforts were made during the early clinical trials of opioid maintenance medications to include female participants, the study populations were overwhelmingly male. In uncomplicated non-opioid-exposed pregnancies, liver enzymes, including AST, ALT and gamma-glutamyl transferase (GGT), show little variation from normal, but it is not known whether opioid agonist medication, HCV exposure or both have an effect on liver enzymes in pregnant opioid-dependent women [23,24]. The Maternal Opioid Treatment: Human Experimental Research (MOTHER) study, a randomized clinical trial designed to examine the efficacy and safety of methadone and buprenorphine in pregnant opioid-dependent women, offers a unique opportunity to examine the effects of both medications on liver enzymes in pregnant women who are maintained on opioid agonist medication. The purpose of the present study is to examine hepatic enzymes throughout the course of pregnancy in HCV-positive and -negative women maintained on methadone or buprenorphine.

This study is a secondary analysis of the MOTHER study medical and pregnancy and postpartum data. The MOTHER study is a multi-site double-blind, double-dummy randomized clinical trial to compare the relative safety and efficacy of methadone versus buprenorphine for the treatment of opioid dependence during pregnancy. Primary and key secondary outcomes have been reported elsewhere [25]. A voucher incentive program was administered as part of the protocol and was effective in minimizing concomitant drug and alcohol use, allowing for clearer analysis of the pharmacotherapeutic effects of methadone and buprenorphine.

Participants

Data were obtained from the 175 opioid-dependent pregnant women who were randomized to either methadone or buprenorphine maintenance in the MOTHER study protocol (methadone $n = 89$, buprenorphine $n = 86$). Participants were aged between 18 and 41 years, carried a singleton pregnancy and were randomized between 6 and 30 weeks' estimated gestational age (EGA), as confirmed by ultrasound. Exclusion criteria included current benzodiazepine or alcohol abuse or dependence as defined by the Structured Clinical Interview of the DSM-IV (SCID) module E, HIV seropositivity, impending incarceration, non-English-speaking (non-German-speaking at the Vienna site) or a medical or psychiatric condition contraindicating study participation as determined by the medically responsible investigator. Participants were not excluded due to elevated transaminase levels. Three participants were excluded from this analysis due to missing laboratory values, resulting in a total of 172 participants. Please see Jones

et al. for a detailed description of participant selection [26].

Procedures

Blood chemistry tests, including liver enzymes and HCV status, were conducted at enrollment and every 4 weeks during pregnancy and once postpartum, 2–6 weeks following delivery.

Data analysis

A total of 402 observations from 172 study participants were utilized in the analyses. A potential 788 data points were reduced to 402 observations (methadone $n = 216$, buprenorphine $n = 186$) by taking arithmetic means of the three trimesters (first trimester 1–12 weeks, $n = 26$; second trimester 13–26 weeks, $n = 143$; third trimester 27–40 weeks, $n = 133$; and the postpartum period, $n = 100$). Three generalized linear mixed models were fitted with dependent variables ALT, AST and GGT levels. Models included fixed effects of medication condition (methadone or buprenorphine maintenance), hepatitis C infection status, pregnancy trimester and their interactions, together with a blocking factor for site [26]. Participant was included in the models as a random effect. Average AST, ALT and GGT levels were taken across pregnancy trimester (1–12, 13–26 and 27–40 weeks EGA), and once at 2–6 weeks' postpartum. A log-link function was utilized, assuming a Poisson distribution and a Huynh–Feldt form error structure.

Table 1 Demographic and health characteristics of the total sample ($n = 172$).

Variable	*Mean (SD)*	*Percentage*
Age	27.3 (5.9)	
EGA week at study entry	17.2 (6.1)	
HCV positive status		38.4%
Injection drug use at study entry		53.1%

EGA: estimated gestational age; HCV: hepatitis C virus; SD: standard deviation.

RESULTS

Of the sample, 38.4% of the participants tested positive for HCV (methadone $n = 36$, buprenorphine $n = 30$). All HCV-positive participants tested positive for HCV infection at screening, with the exception of one participant who converted to HCV-positive status during study participation in the third trimester. Fifty-three per cent of the participants were injection drug users (Table 1).

AST, ALT and GGT level means are displayed by trimester in Table 2. Thirteen participants (7.6%; methadone $n = 8$; buprenorphine $n = 5$) had at least one laboratory value three times the upper limit of normal (ALT = 120, AST = 105 or GGT = 180). AST and ALT levels were significantly higher in the postpartum period than in either the second (ALT: $t_{(268)} = -3.8$, $P = 0.0002$; AST: $t_{(265)} = -3.2$, $P = 0.001$) or third trimesters (ALT: $t_{(251)} = -4.4$, $P = 0.0001$; AST: $t_{(230)} = -3.0$, $P = 0.003$) of pregnancy. ALT levels were also higher in the first versus third trimester of pregnancy ($t_{(274)} = 2.2$; $P < 0.05$). First-trimester GGT levels were significantly higher than in subsequent trimesters or the postpartum period, displaying a decreasing trend over the course of pregnancy; $P < 0.001$ for second ($t_{(270)} = 3.6$; $P = 0.0003$) and third trimesters ($t_{(304)} = 3.7$; $P = 0.0003$). However, levels of GGT appear to increase again in the postpartum period, with GGT being significantly higher postpartum than in the third trimester ($t_{(194)} = -3.0$; $P = 0.003$).

Participants who were positive for HCV infection had higher ALT, AST and GGT levels at all time-points, and it was found that trimester modified the effect of HCV, with HCV-positive subjects having higher transaminases in the first ($F_{(1,240)} = 14.9$, $P = 0.0001$) and third trimesters ($F_{(1,194)} = 5.5$, $P = 0.02$) and a trend towards significance for the second trimester ($F_{(1,190)} = 3.3$, $P = 0.07$). Figures 1 and 2 show the mean ALT, AST and GGT levels by HCV infection status over the course of pregnancy for buprenorphine and methadone, respectively. Overall, HCV-positive participants exhibited higher ALT, AST and GGT levels at each time-point, with levels being twice as high as HCV-negative patients in the first trimester. Levels for ALT, AST and GGT decreased over the second and third

Table 2 Means of total sample for AST, ALT and GGT levels by trimester ($n = 172$).

Trimester		*AST*		*ALT*		*GGT*	
Observations		*mean (SE)*	*CI*	*mean (SE)*	*CI*	*mean (SE)*	*CI*
1st	26	31.3 (4.4)	23.7–41.3	33.5 (5.4)	24.3–46.0	27.9 (4.1)	20.8–37.4
2nd	143	26.1 (1.7)	22.9–29.7	25.2 (2.0)	21.5–29.5	16.1 (1.6)	13.2–19.5
3rd	133	26.7 (1.7)	23.6–30.3	23.6 (2.3)	19.5–28.6	15.8 (1.7)	12.9–19.5
PP	100	32.9 (1.8)	29.6–36.7	36.3 (3.0)	30.8–42.8	20.3 (2.1)	16.5–25.0

ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: gamma-glutamyl transferase; PP: postpartum; SE: standard error; CI: confidence interval; normal range ALT: 0–40 IU/l, AST: 5–35 IU/l, GGT: 0–60 IU/l.

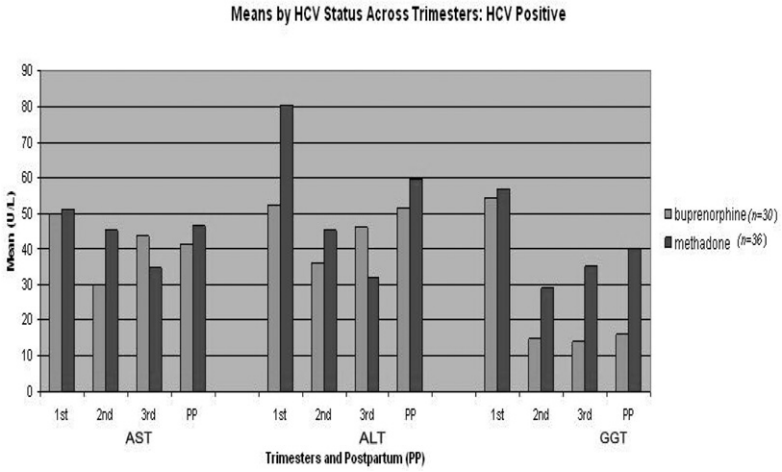

Figure 1 Means by hepatitis C virus (HCV) status across trimesters: HCV-positive ($n = 66$)

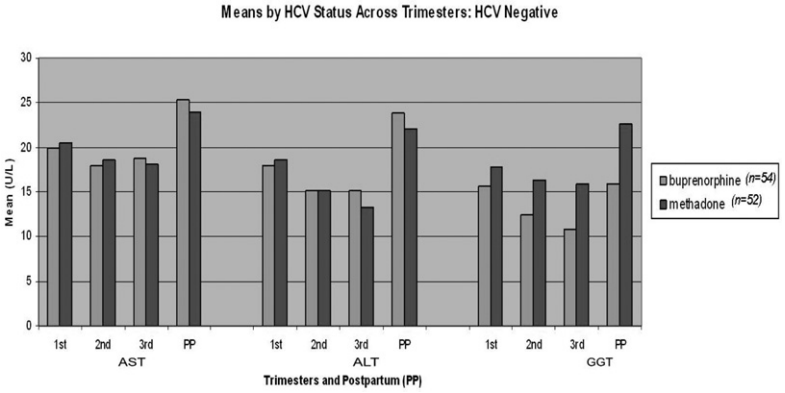

Figure 2 Means by hepatitis C virus (HCV) status across trimesters: HCV-negative ($n = 106$)

Table 3 Tests of significance for fixed effects ($n = 172$).

	AST		*ALT*		*GGT*	
Effect	*(d.f.) F*	*P*	*(d.f.) F*	*P*	*(d.f.) F*	*P*
Medication	(1, 186) 0.4	0.6	(1, 200) 0.5	0.5	(1, 167) 8.8	0.004
HCV	(1, 193) 48.1	≤0.001	(1, 207) 60.7	≤0.001	(1, 286) 7.7	0.001
Trimester	(3, 272) 4.4	0.005	(3, 264) 7.9	≤0.001	(3, 238) 7.7	≤0.001
Medication × HCV	(1, 199) 0.7	0.4	(1, 211) 1.3	0.3	(1, 188) 1.9	0.2
Medication × trimester	(3, 272) 1.9	0.1	(3, 262) 1.6	0.2	(3, 236) 1.5	0.2
HCV × trimester	(3, 272) 0.8	0.5	(3, 264) 0.4	0.8	(3, 239) 3.4	0.02
Medication × HCV × trimester	(3, 273) 1.2	0.3	(3, 265) 0.8	0.5	(3, 239) 0.4	0.8

ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: gamma-glutamyl transferase; HCV: hepatitis C virus. Medication: randomization to either methadone or buprenorphine maintenance.

trimesters for both HCV-positive and -negative patients, increasing in the postpartum period. HCV-positive patients showed a more marked decrease in the second and third trimesters compared to HCV-negative patients.

Medication condition (whether a participant was randomized to maintenance with buprenorphine or methadone) affected GGT levels ($F_{(1,167)} = 8.8$, P = 0.004) significantly, with methadone-maintained patients exhibiting higher GGT levels than buprenorphine-maintained patients. Medication condition did not influence ALT or AST levels (ALT: $F_{(1,200)} = 0.5$, $P = 0.5$; AST: $F_{(1,186)} = 0.4$, $P = 0.6$). The interaction term between medication condition and HCV infection status was not significant for ALT, AST or GGT levels (Table 3), indicating that the maintenance medication did not differentially affect liver enzyme levels significantly according to HCV-positive or -negative status. The interaction term between medication and pregnancy trimester was also

non-significant for ALT, AST and GGT levels, suggesting that the effects of medication condition do not differ according to trimester (Table 3).

DISCUSSION

In this analysis of the MOTHER data we examined the transaminases ALT, AST and GGT, as these enzymes have been considered surrogate measures of liver inflammation and/or injury when patients are treated with buprenorphine. Further, we compare effects of the two most commonly used medications for treating opioid dependence on these enzymatic markers of liver function in a specialized population of HCV-positive and -negative pregnant opioid-dependent women.

The effect of opioid dependence on surrogate liver function tests in pregnancy is not a well-studied topic. In healthy uncomplicated pregnancies, the transaminases ALT and AST are generally unaffected or slightly lower compared to non-pregnant values [23,24], and are normally less than 40 IU/l. During the course of pregnancy, transaminase levels may decrease somewhat. The literature is less definitive for GGT, but it appears that levels are generally below 50 IU/l in healthy pregnancies [24]. The only hepatic enzyme noted to increase during the course of normal pregnancy is alkaline phosphatase, which is not specific to the liver as it is also produced in other organs [23].

Mean hepatic transaminases values were within normal limits in the first trimester and remained so throughout the pregnancy and the postpartum period for the total sample. The level of GGT decreased significantly during the course of the pregnancy, and all three transaminases appeared to increase slightly during the postpartum period while remaining within the clinically normal range.

Patients who have been exposed to HCV are more likely, at least intermittently, to have elevated transaminase levels. Approximately one-third of the study population was HCV-positive, and these patients had significantly higher transaminase levels across all three trimesters and postpartum, irrespective of medication group, when compared to HCV-negative patients. Although the participants who were HCV-positive had higher transaminase levels, they appeared to trend towards normal during the course of pregnancy with both methadone and buprenorphine maintenance, suggesting that neither drug appeared to have a deleterious effect on liver enzymes. However, participants treated with buprenorphine were more likely to have lower GGT levels than those treated with methadone, whether they were HCV-positive or -negative. HCV-negative participants had normal transaminase levels throughout pregnancy and in the postpartum period, regardless of whether medicated with methadone or buprenorphine, again supporting the safety of both opioid therapies from a hepatic standpoint.

These results are not consistent with the findings of Petry *et al.*, where increases in both AST and ALT were noted after buprenorphine exposure; GGT was not analyzed in the Petry study [12]. There are several reasons why these data may differ from previous findings. The Petry *et al.* sample was primarily male, with an average age of 42 years compared to an average age of 27 years in our sample of pregnant women. Additionally, the majority of the Petry *et al.* sample was HCV-positive, while only one-third of our participants were positive for HCV, due potentially to the number of participants in our sample who abused prescription opioids prior to study entry, and were not injection drug users. The lower average age and prevalence of HCV infection, as well as the fact that the subjects were pregnant in our study relative to the Petry *et al.* sample, may indicate pre-existing differences in the general health of the liver between the two study populations.

Although this study is limited by sample size and numbers of observations, these data indicate that pregnant, opioid-dependent women treated with buprenorphine or methadone do not exhibit liver toxicity or exacerbation of underlying liver disease (HCV). In fact, it appears that as pregnancy progressed, both medications were associated with a reduction of serum hepatic enzymes. Such a reduction in transaminases could be due to the effects of reduced drug and/or alcohol use in the context of the opioid agonist treatment and voucher incentive program available in this study, as well as the normal effect of pregnancy on the enzyme levels.

While our data demonstrate that there are no detrimental hepatic effects of either buprenorphine or methadone, there are limitations to this study. First, a voucher incentive program was utilized very effectively to reduce the use of all illicit drugs, limiting our ability to generalize about the effects of either medication in a population with ongoing substance abuse. Secondly, women diagnosed with alcohol or benzodiazepine abuse or dependence were excluded from the study, but there was sporadic use of these drugs of abuse. The combination of HCV infection and alcohol abuse is highly detrimental to the liver. It is not known if buprenorphine or methadone would be differentially beneficial or toxic in cases of HCV infection and ongoing alcohol abuse, or if use of either medication would exacerbate the underlying liver disease. Further research is needed to provide additional data on the effects of buprenorphine and methadone on liver enzymes in pregnant and non-pregnant women who are opioid-dependent. However, this study provides further information on the safety of both methadone and buprenorphine for the treatment of opioid dependence in pregnancy.

Clinical trial registration

The clinical trial was registered with ClinicalTrials.gov (Identifier: NCT00271219; title: RCT Comparing Methadone and Buprenorphine in Pregnant Women.

Declarations of interest

MOTHER Study

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Reckitt Benckiser Healthcare, Hull, UK supplied buprenorphine tablets (and the associated placebo) via NIDA. Neither Reckitt Benckiser nor NIDA had any involvement in study design, data collection, analysis, interpretation, or manuscript preparation.

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K. O'G. discloses that he has received reimbursement for time from Reckitt Benckiser.

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No additional declarations of interest.

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