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Original Research Article

The effects of antibiotics on liver enzymes in pregnancy

Kanika Handu*, Sujatha Prabhu

Department of Obstetrics and Gynecology, ESIC Medical College and PGIMSR, Rajajinagar, Bengaluru, Karnataka, India

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***Correspondence:**
Dr. Kanika Handu,
E-mail: handukanika@gmail.com

ABSTRACT

Background: Antibiotics are increasingly being prescribed during pregnancy. Even though safe non-teratogenic drugs are prescribed, due to altered pharmacokinetics during pregnancy can have adverse effects on hepatic metabolism.
Methods: This was a prospective analytical study conducted in the department of obstetrics and gynecology at ESIC Medical College and PGIMSR, Bengaluru, Bengaluru from August 2022 to January 2023, 62 pregnant women diagnosed with infection were admitted and evaluated for the effects of antibiotics on liver enzymes. All cases had undergone a baseline Liver function test before antibiotic therapy were compared and statistically analyzed with the liver enzymes, alanine transaminase (ALT), and aspartate transaminase (AST) values after 7 days of the antibiotic course.
Results: In this study, the mean age of pregnant women enrolled was 26±3.62 years. Both primi (45.2%) and multigravida (54.8%) were equally represented. The most commonly prescribed antibiotic was cefotaxime (67.7%). The mean pre AST was 17.92±11.28 and post-AST was 18.34±15.55 U/l (paired t-test =0.861) and the mean pre-ALT was 13.09±19.82 and post-AST was 11.7±8.01 U/l (paired t-test =0.533). Hence there were no significant changes in post-AST and post-ALT compared to Pre AST and ALT values.
Conclusions: In this study the common antibiotics administered were cephalosporins and they didn't show any effects on AST or ALT values after completing the antibiotic course.

Keywords: ALT, Antibiotics, AST, Pregnancy

INTRODUCTION

Infections in pregnancy are associated with significant morbidity. The rate at which antibiotics are being taken is increasing rapidly (26.1%).[1] Antibiotic exposure in pregnancy has both short-term and long-term effects. Only 10% of medications have sufficient data on safe and effective use in pregnancy.[2]

Drug-induced liver injury (DILI) is a rare but potentially threatening consequence of drug administration during pregnancy.[3] Even though nonteratogenic drugs are prescribed in pregnancy, rarely they have hepatotoxic effects.[1]

Antibiotics like beta-lactams are considered safe while fluoroquinolones and tetracyclines are avoided in pregnancy.[4] Physiological changes in pregnancy increase the glomerular filtration rate, total body volume, and cardiac output. This leads to altered pharmacokinetics of antibiotics which requires dose adjustment and careful monitoring and assessment.[5]

Underreporting of adverse drug reactions has led to difficulty in diagnosing DILI during pregnancy which makes the management challenging.[1]

Therefore, it has become important to investigate the effects antibiotics have on the liver, by monitoring the

levels of the ALT and AST in the serum of pregnant individuals on antibiotics. The need of the study was to provide information in the direction of the appropriate use of antibiotic agents by highlighting the effects of the antibiotics.

METHODS

A prospective analytical study was conducted on 62 pregnant women on treatment with antibiotics at ESIC medical college and PGIMSR, Rajajinagar, Bangalore from August 2022 to January 2023.

This study was performed after obtaining ethical approval from the institutional ethical committee and informed written consent obtained from all the participants.

The sample size was calculated using the following formula considering a 20% proportion with increased AST and ALT with the power of 80%, 95% confidence interval with a relative precision of 10%. The sample size is equal to 62.

$n= z^2p(1-p)/d^2$

Where Z= z statistic at a 5% level of significance

d is the margin of error

p is the anticipated prevalence rate

Inclusion criteria

62 pregnant women admitted to the antenatal ward in the department of obstetrics and gynecology for antibiotic therapy with a relevant indication (in all trimesters) were recruited in the study.

Exclusion criteria

Pregnant women with pre-existing liver diseases. Pregnant women who were on anti-glycemic, antihypertensive, anti-thyroid, antiretroviral, and anti-tubercular drugs. Pregnant women who were already on antibiotics before the time of their inclusion in the study.

Methodology

All participants were clinically evaluated with demographic characteristics, detailed medical history, obstetric score, and period of gestation supported by clinical and laboratory investigations.

Specific investigations like urine culture and sensitivity, high vaginal swab culture and sensitivity were done in indicated cases based on symptomatology and clinical diagnosis of systemic infection.

All recruited pregnant women had baseline liver function tests performed to determine the AST and ALT levels before administration of antibiotics and the same was repeated immediately after completion of the course of antibiotics within 7 days.

All were clinically followed up with appropriate antenatal care.

SPSS V21 Statistical software was used to analyze the data.

Collection of blood sample

After taking informed consent, under aseptic precautions, 2 ml of venous blood sample was drawn and then transferred to plain sterile vacutainer tubes. Blood was allowed to clot at 37℃ and then centrifuged at 3000 rpm for 10 minutes to separate the serum, the sera thus separated was transferred to plain bullet vials and used for the analysis of liver enzymes- AST and ALT.

Estimation of AST BY ROCHE COBAS integra 400 Plus

ALT catalyses the reaction between L alanine and 2 oxoglutarate. The pyruvate formed is reduced by NADH in a reaction catalysed by lactate dehydrogenase to form L lactate and NAD. The rate of NADH oxidation is directly proportional to the catalytic ALT activity. It was determined by measuring the decrease in absorbance at 340nm.

Abnormal LFT was defined as at least one result of the two markers (ALT/AST) greater than its upper limit of normal (ULN), that is ALT>40 U/l or AST>40U/l.

RESULTS

This study was conducted in the department of obstetrics and gynecology at ESIC medical college and PGIMSR. The objective was to know the effects of antibiotics on liver enzymes in pregnancy.

62 pregnant women diagnosed with maternal infections such as UTI, URTI, etc. who required admission and administration of antibiotics therapy meeting the inclusion and exclusion criteria were recruited for this study.

Table 1: Age distribution of the subjects.

Age groups	Number	Percentage
20-24 years	23	37.1
25-29 year	33	53.2
>30 years	6	9.7
Total	62	100

The mean age of pregnant women enrolled in the study was 26±3.62 years.

Table 2: Obstetric score of study subjects according to parity.

Parity	Number	Percentage
Multi	34	54.8
Primi	28	45.2

Both primi (45.2%) and multigravida (54.8%) were almost equally represented.

Table 3: Comparison of serum AST values before and after antibiotic therapy.

Liver enzymes	Mean	SD	Paired t-test
Pre AST	17.92	11.28	0.861
Post AST	18.34	15.55	

There was no significance in the serum values of AST following the completion of the antibiotic course.

Table 4: Comparison of serum ALT values before and after antibiotic therapy.

Liver enzymes	Mean	SD	Paired t-test
Pre ALT	13.09	19.82	0.533
Post ALT	11.70	8.01	

There was no significance in the serum values of ALT following the completion of the antibiotic course.

Table 5: The pharmacological category of antibiotics used during pregnancy in the study.

Drugs	Number of pregnant women on respective antibiotics (n)	Number of pregnant on respective antibiotics (%)
Cefotaxime	43	69.4
Amoxiclav	12	19.4
Metronidazole	6	9.7
Penicillin	1	1.6

Table 6: Effect of antibiotics used during pregnancy on AST levels.

Drugs	Pre AST Mean±SD (U/l)	Post AST Mean±SD (U/l)	P value
Cefotaxime	17.80±11.46	19.37±18.24	0.633
Amoxiclav	18.43±13.40	16.57±6.90	0.580
Metronidazole	19.12±6.42	15.12±4.42	0.247
Penicillin	10.10	14.90	

The pharmacological category of antibiotics used during pregnancy also did not have any significant rise in levels of AST following the completion of the antibiotic course (Table 6).

Table 7: Effect of antibiotics used during pregnancy on ALT levels.

Drugs	Pre ALT Mean±SD (U/l)	Post ALT Mean±SD (U/l)	P value
Cefotaxime	12.73±22.31	10.72±4.86	0.523
Amoxiclav	16.05±15.89	16.93±14.90	0.741
Metronidazole	10.95±4.72	8.75±3.25	0.305
Penicillin	6.20	9	

The pharmacological category of antibiotics used during pregnancy also did not have any significant rise in levels of ALT following the completion of the antibiotic course.

DISCUSSION

Antibiotics constitute wide systemic usage in treating infections in pregnancy for urinary infection, upper respiratory tract infection, and as prophylaxis in cesarean delivery, preterm pre-labor rupture of membranes, and for delivery etc.[5]

Drugs considered safe for use in pregnancy are known to cause idiosyncratic DILI.[6] Co-morbidities like malnutrition, obesity, diabetes, and pre-existing liver disease may further intensify the risk of DILI during pregnancy.[7] Drug factors like pharmacological class, dosage, and polypharmacy could also contribute.[8]

In studies where specific drug use has a higher risk of hepatotoxicity in pregnant women compared with non-pregnant women, the mechanisms underlying the increased risk are unclear.[9] It is to be noted that in such cases, it is pregnancy rather than the drug, which is a risk factor for hepatotoxicity, suggesting that the changes that occur during the pregnancy influence the likelihood of a drug causing hepatic damage.[10]

In 2020, Low et al conducted a meta-analysis on drug-induced liver injury: East versus West. It was concluded that in the west, amoxicillin-clavulanate, nimesulide, and ibuprofen are common agents implicated in DILI while in East INH-RIF-PZA, cephalosporins, and phenytoin.[4]

DILI is one of the factors associated with mortality and chronic liver injury, although a majority of the cases will resolve on withdrawal of the drug or the diagnosis will be missed due to the relatively transient disturbance.[8]

DILI is one of the least studied aspects of pregnancy. Most of the available literature is in the form of case reports.[2] A study in the UK found that drugs accounted for 2.8% of abnormal liver function tests in pregnant women.[1] Difficulty in diagnosis due to underreporting and spontaneous resolution after the inciting drug is discontinued is likely to account for missing out on such cases.[1]

Liver injury due to drugs may be direct or indirect or Idiosyncratic.[11] Clinical manifestations range from asymptomatic deranged liver function to fulminant hepatic failure and death.[12] The time of onset after drug exposure varies from hours to months. The spectrum of clinical presentation with DILI is broad ranging from asymptomatic elevation in liver enzymes to non-specific symptoms characterized by malaise, abdominal pain, and nausea to jaundice, pruritus, and encephalopathy.[10]

During normal pregnancy except for ALP and 5 nucleotides most values of serum routine LFT remain below the upper limits established in non-pregnant women.[13] Any increase in serum AST and ALT, serum bilirubin, serum GGT or fasting bile acid concentration should be considered pathologic and should prompt further evaluation to diagnose the causality of liver dysfunction.[14]

This study aimed to evaluate the effects of antibiotics on liver enzymes, specifically AST and ALT, in pregnant women. The results showed that there were no significant changes in AST and ALT levels after a 7-day course of antibiotics. These findings suggest that the use of antibiotics in pregnancy did not have a significant impact on liver enzyme levels in the studied population.

However, one case had significant raise in the liver enzymes above the upper limit of the normal after the cefotaxime course, which gradually returned to normal levels in the subsequent weeks after routine care and monitoring. This finding suggests that there may be individual variations in liver enzymes' response to antibiotics during pregnancy. It further emphasizes the importance of careful monitoring and follow-up to assess the impact of antibiotics on liver function in pregnant individuals.

Administration of cephalosporins via the parenteral route may result in mild, temporary increases in serum levels of aminotransferase and alkaline phosphatase, without any associated symptoms or progression to severe liver damage.[15] In this study cephalosporins (69.4%) was the most commonly used drug followed by amoxiclav (19.4%), metronidazole (9.7%) and penicillin (1.6%). However, the drugs used in the study had no significant effects on the AST and ALT values after the antibiotic course.

It is worth noting that the study had certain limitations, including a small sample size and a short duration of follow-up. The short-term nature of the study may not capture the potential long-term effects of antibiotics on liver enzymes during pregnancy.

While the present study did not find significant changes in liver enzyme levels following antibiotic use in pregnancy, further research with larger sample sizes and longer follow-up periods is needed to provide more conclusive evidence on the effects of antibiotics on liver function during pregnancy. It is essential to consider potential confounding factors and evaluate the risks and benefits of antibiotic use in pregnancy on a case-by-case basis.

CONCLUSION

According to the present study, there were transient changes in the liver enzymes during pregnancy which were not significant. However, as the exclusion criteria eliminated other causes of liver dysfunction and confounding factors, the presence of these transient changes signifies the need for more cautious use of antibiotics in pregnancy.

Since the study was limited to a small sample size and short duration of study no cases with drastic changes in liver enzymes could be found. More evident results require a study with a larger sample size and a longer duration of study and follow-up of patients to state the longer-term effects of antibiotics on liver enzymes in pregnancy.

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