Print ISSN: 2319-2003 | Online ISSN: 2279-0780

IJBCP International Journal of Basic & Clinical Pharmacology

DOI: http://dx.doi.org/10.18203/2319-2003.ijbcp20173760

Original Research Article

Study of analgesics usage in third trimester of pregnancy and its ill effects on pregnancy course and outcome

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Received: 12 July 2017
Revised: 18 July 2017
Accepted: 05 August 2017

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ABSTRACT

Background: Pregnancy is a special physiological state. Pregnancy care is one of the greatest challenges in medicine as it demands a special care in the use of drugs because of altered physiology. At least 10 percent of birth defects are thought to result from maternal drug exposures. NSAIDS are one of the most commonly used medications during pregnancy (17%) to treat painful events during pregnancy.
Methods: A prospective observational study was conducted after taking approval from the Institutional ethical committee and study was conducted for a period of one year. Antenatal clinics and inpatients wards of department of obstetrics and Gynaecology were visited and all the pregnant women with exposure to analgesics during third trimester and at the time of labour were included in the study. Information regarding the analgesics exposure either prescribed by the physician or self-medicated was collected.
Results: Total 1520 pregnant women were included in the study over a period of one year. Analgesic exposure was seen in 77.1% of pregnant women during labour. Most common analgesic used to relieve labour pain was tramadol. 22.9% pregnant women were exposed to analgesics during third trimester, among them exposure to paracetamol was observed in 14% of pregnant women and to tramadol in 8.9%. Indications for usage of these analgesics during pregnancy were fever with myalgia (45.8%), false labour pain (37%), and headache (11.4%).
Conclusions: Study showed that there is a positive association between analgesics exposure during third trimester of pregnancy particularly to paracetamol exposure and preterm delivery. Association between paracetamol exposure and low birth weight was also observed in this study but this finding could be due to more number of preterm deliveries which could not be ruled out in this study. Further studies have to be conducted to confirm the association since there are only limited numbers of studies done till now.

Keywords: Analgesics, Pregnancy third trimester

INTRODUCTION

Pregnancy is a special physiological state.[1] Pregnancy care is one of the greatest challenges in medicine as it demands a special care in the use of drugs because of altered physiology.[2,3] At least 10 percent of birth defects are thought to result from maternal drug exposures.[4] The issue is complicated by the fact that the safety and efficacy profile of a given medicine often changes during the course of a normal pregnancy.[5] NSAIDS are one of the most commonly used medications during pregnancy (17%) to treat painful events during pregnancy.[6]

During pregnancy, pain may be caused by acute conditions such as injury or infection, or secondary to underlying medical disorders. Pregnancy related pain can also occur. Many of analgesics are prescribed irrationally due to lack of awareness among the doctors. Analgesics belonging to

Category C, D and X drugs are easily available without prescription and abused by the expecting mothers without the knowledge of their ill effects.[7] Ill effects of usage of NSAID analgesics in first trimester of pregnancy are well known, use of NSAIDS is contraindicated because of their potential to cause premature closure of the fetal ductus arteriosus and persistent pulmonary hypertension.[8] Use of opioids persistently may result in dependence and tolerance in the mother with resultant withdrawal (neonatal abstinence syndrome) in the neonate.[8] Due to easy availability of drugs and inadequate health services in India, increased percentage of drugs are used as self-medication as compared to prescribed drugs.[9]

Many studies are done to assess the ill-effects of analgesics usage in first and second trimester of pregnancy, but only a limited number of studies are done to assess ill-effects in last term. Hence studies are required to assess usage of analgesics and their ill effects if any and to implicate them for their ill effects on pregnancy course and outcome.

METHODS

A prospective observational study was initiated after approval and the study was done over a period of one year. All the women in third trimester attending ante natal clinic and those admitted to antenatal ward and labour room of Medical College Teaching Hospital, Mandya were enrolled for the study, after explaining the study requirement in the language they understand and after obtaining written informed consent.

OPD of ante natal clinic was visited, pregnant women in the third trimester of pregnancy were enquired regarding any painful events in the third trimester and any history of intake of analgesics during third trimester either prescribed or self-medicated. If they give the history of intake, she was enquired regarding any adverse events after intake of analgesics. If the patient is prescribed analgesics for the first time in the present antenatal visit, it was noted down and both the types of cases were followed up till the delivery of the patient, to know any adverse pregnancy outcomes. Data was also collected regarding subject's demography, obstetric, menstrual personal, family history and detailed history regarding usage of analgesics in the third trimester either prescribed or self-medicated by the patient, reason for use, and period of gestation in weeks during exposure to analgesics and also data regarding concomitant drug use was collected in a predesigned proforma.

Among the pregnant women in the inpatient wards, those who were prescribed with analgesics were included in the study. Indication for prescription of analgesics was noted and pregnant women were also asked for any self-medication of analgesics during 3rd trimester. Any episodes of adverse reaction immediately after the intake of analgesics was noted and followed till delivery. Pregnant women who were admitted in the labour room were also asked regarding the history of analgesic intake in the recent past and analgesics used during labour was noted down. Prescriptions was collected and compiled. History of concomitant medication administered during third trimester and labour as per the case record was collected. Information on the pregnancy course and outcome as recorded in the case records was collected and was entered and compiled in excel sheet.

Statistical methods

Data entry and analyses were done using the Statistical Package for Social Sciences (SPSS) for Windows software (version 20.0; SPSS Inc). Descriptive statistics such as mean and standard deviation (SD) for continuous variables, and frequency and percentage for categorical variables were determined. The chi-square test and fisher's exact test (where appropriate) was used to show the associations between predictor and outcome variables.

The level of significance was set at 0.05. Factors associated with pregnancy outcome of patients were determined at both univariable and multivariable level using simple logistic regression analysis and multiple logistic regression analysis respectively. In multiple logistic regression analysis, variables for inclusion in the model were selected using forward stepwise logistic regression methods.

RESULTS

Total of1520 pregnant women were included in the study to evaluate the usage of analgesics during 3rd trimester of pregnancy and its effect on the course and outcome of pregnancy. Majority of pregnant women were in the age group of 21-25 years and mean age was 23.7±3.2 years (Figure 1).

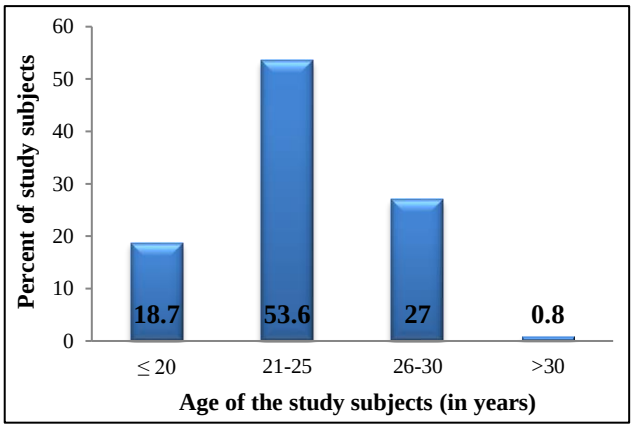

Figure 1: Distribution of subjects according to their age.

In this study about 60% of pregnant women were primigravida and only 40% were multigravida (Figure 2).

Mean gestation period of study subjects was 37.7±2.8 weeks and the range was 28-43 weeks (Figure 3).

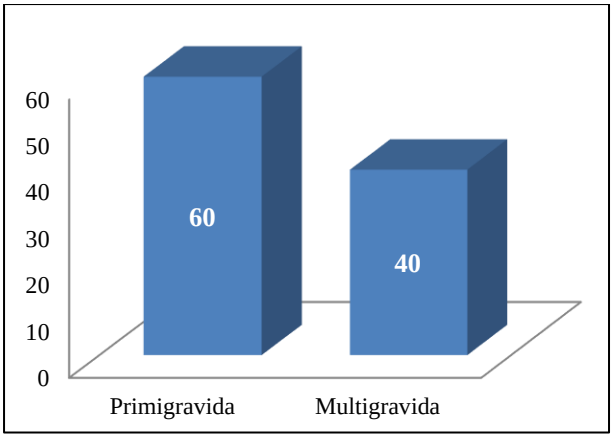

Figure 2: Distribution of subjects according to obstetric score.

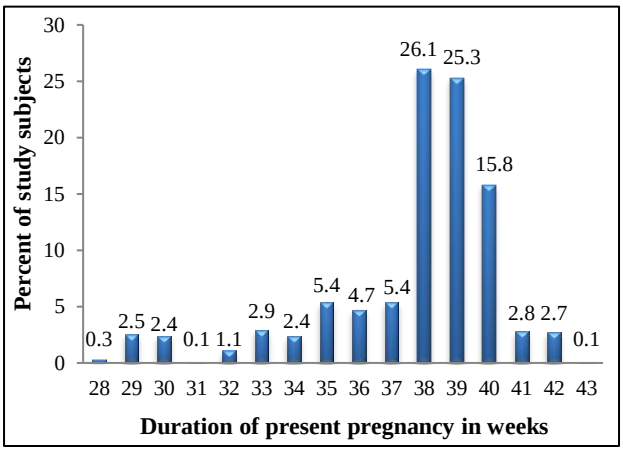

Figure 3: Distribution of patients according to POG of present pregnancy.

Table 1: Distribution of study subjects according to the Obstetric and Medical disorders during present Pregnancy (N = 1520).

Disorders during present pregnancy	No.	Percentage
Anaemia	45	3.0
GDM	10	0.7
HIV	1	0.1
Hypothyroidism	2	0.1
IUGR	39	2.6
Oligohydramnios	59	3.9
PIH	27	1.8
Polyhydramnios	8	0.5
PPROM	4	0.3
PROM	16	1.1
RH-ve	16	1.1
RHD	7	0.5
Septate Uterus	1	0.1
URTI	1	0.1
UTI	3	0.2

Out of 1520 pregnant women only 239 (15.7%) had associated medical and obstetric complications. Anaemia was the most common medical condition complicating pregnancy in our study (Table 1).

In majority of subject's analgesics were used during labour to relieve labour pain. Only 21.1% used analgesics during 3rd trimester of pregnancy. Analgesic used during 3rd trimester of pregnancy includes both prescribed and over the counter drugs (Table 2).

Table 2: Distribution of study subjects according to time of analgesics used (N=1520).

Time of analgesic usage	Percentage
Only during pregnancy	21.1
Only during labour	77.1
Both during pregnancy and labour	1.77

Among the analgesic used during pregnancy, 14% used Paracetamol and Tramadol was used by 8.9% of pregnant women (Figure 4).

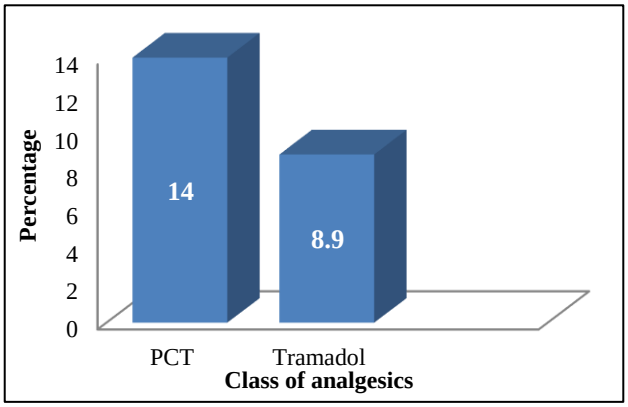

Figure 4: Distribution of subjects according to class of analgesics used.

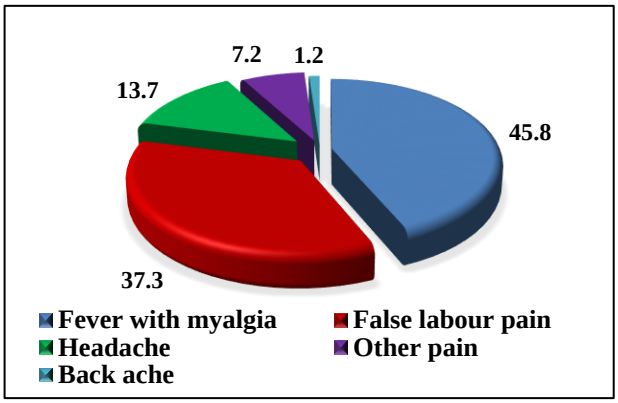

Figure 5: Indication for usage of analgesics during pregnancy.

Main indication for use of analgesics in majority of study subjects was fever with myalgia followed by false labour pain (Figure 5).

Paracetamol was used for relief of pain associated with fever, for headache and for other types of aches. Main indication for use of Tramadol during pregnancy was false labour pain. Out of the total analgesics used during pregnancy, 93. 1% was prescribed by doctors and 6.9% was self-medicated by study subjects for minor ailments (Figure 6).

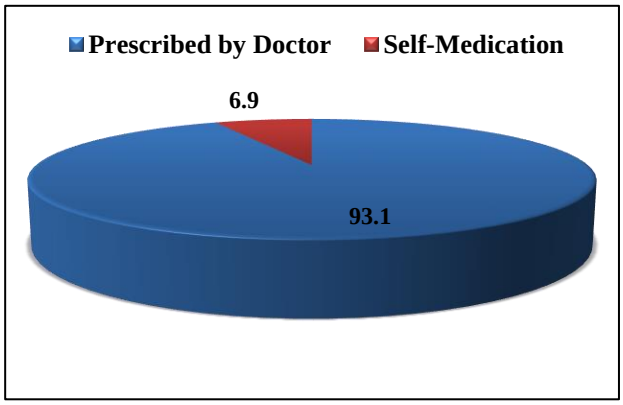

Figure 6: Distribution of subjects according to pattern of usage of analgesic.

Among study subjects, preterm deliveries were found to be more in those who were exposed to analgesics during third trimester of pregnancy. Percentage of preterm delivery was more among those exposed to paracetamol than those who were exposed to tramadol with P-value <0.001 which is statistically significant (Figure 7).

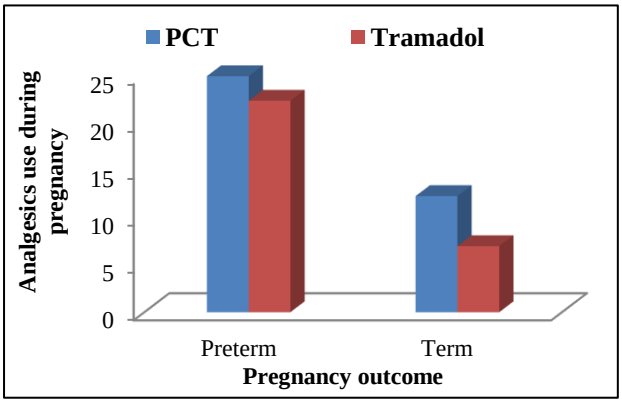

Figure 7: Association between analgesics used during pregnancy and outcome of pregnancy.

Percentage of low birth weight was more in those pregnant women who have used analgesics during pregnancy than who have not used it and percentage of association is more with paracetamol exposure than with tramadol (Figure 8).

Tramadol is used to relieve labour pain more in term deliveries than preterm delivery (Figure 9). Nausea and vomiting were the most common adverse drug reactions among pregnant women who have used tramadol when compared with those who used paracetamol (Table 3) (Figure 10).

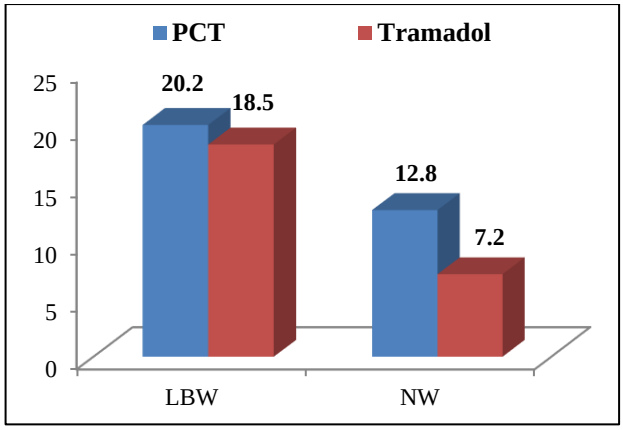

Figure 8: Association between analgesics used and birth weight of the newborn.

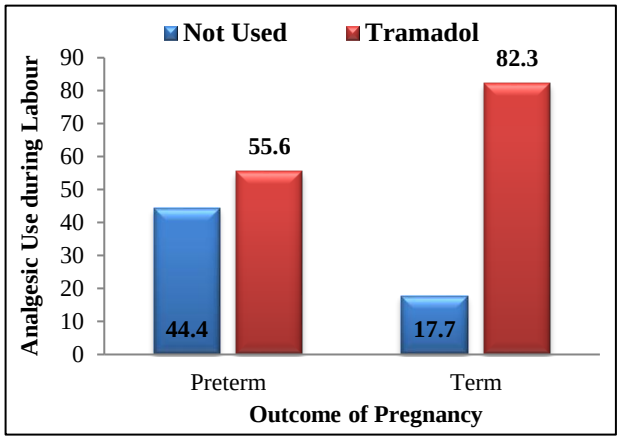

Figure 9: Indication for use of analgesics during labour.

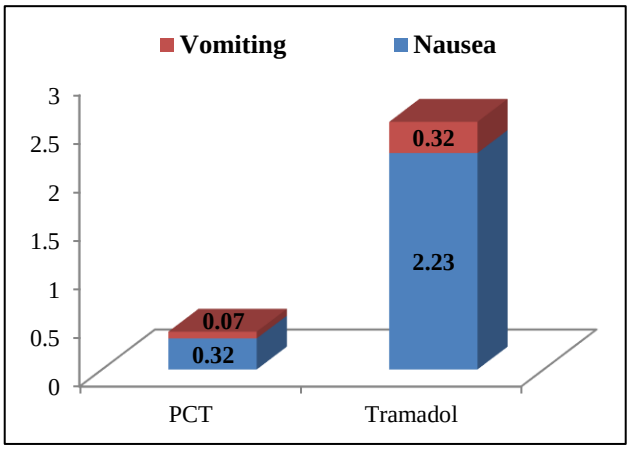

Figure 10: Association between use of analgesics and adverse drug reactions.

Multiple logistic regression analysis of study population showed that there is association between analgesic usage during pregnancy preterm delivery with odds ratio 0f 3.66 and 95% CI of 2.69-5 (Table 4).

Table 3: Distribution of study subjects according to the Adverse Drug Reactions Reported (N = 1250).

ADR reported	No.	Percent
Nausea	39	2.57
Vomiting	6	0.4
Drowsiness	0	0.0
PPH	0	0.0
APH	0	0.0

Table 4: Independent predictors of preterm delivery using multiple logistic regression analysis.

Predictor variables	Odds ratio	95% C.I.
Maternal Age >30 years	10.74	1.48-77.82
Age at Menarche >12 years	1.56	1.15-2.12
Multigravida	2.80	1.96-4.00
Multipara	2.74	1.87-4.02
More than 1 living child	3.15	2.11-4.69
Having abortions	1.55	0.82-2.95
Analgesic used during pregnancy	3.66	2.69-5.00
Analgesic used during labour	3.60	2.63-4.93
Frequency of analgesic use during pregnancy more than once	1.29	0.80-2.09
Self-medication during pregnancy	0.90	0.35-2.36
More than 2 concomitant drugs used during pregnancy	2.33	1.16-4.66

Table 5: Independent predictors of low birth weight using multiple logistic regression analysis.

Predictor variables	Odds ratio	95% C.I.
Maternal Age >30 years	4.14	1.29-13.29
Age at Menarche ≤12 years	1.50	1.13-2.00
Multigravida	1.88	1.38-2.56
Multipara	1.74	1.26-2.39
More than 1 living child	1.95	1.40-2.71
Having abortions	1.38	0.78-2.46
Previous pregnancy mode of delivery as FTND	0.45	0.31-0.66
Analgesics used during pregnancy	2.52	1.86-3.37
Analgesics used during labour	2.59	1.89-3.45
Frequency of analgesics used during pregnancy more than once	1.03	0.63-1.67
Self-medication during pregnancy	1.35	0.48-3.73
More than 2 concomitant drugs used during pregnancy	2.82	2.03-3.33

Multiple logistic regression analysis for low birth weight showed that there is association between analgesics usage during pregnancy and low birth weight with odds ratio of 2.52 and 95% CI of 1.86-3.37 (Table 5).

DISCUSSION

Since pregnancy is associated with significant physiologic changes that have potential to alter the medication selection and dosage, intelligent use of drugs during pregnancy requires that, physician understands the interaction between drugs and pregnancy so that indiscriminate use of drugs resulting in disastrous consequences may be avoided.

Many pregnant women tend to take over the counter drugs for minor ailments during pregnancy which will have a deleterious effect on the developing foetus depending on the age of gestation they are used. Drug treatment may be unavoidable during pregnancy but it will inevitably expose the unborn child to the effects, whether pharmacological or toxic effects of the drug. Thus Drugs given during pregnancy must be for the benefit of the mother without producing unwanted complication to the developing foetus. Use of over the counter drugs should be discouraged among pregnant women. Before exposing the pregnant women to drugs certain aspects and principles have to be considered so that the drugs given are safe, rational and scientifically sound.

Present study was a prospective observational study undertaken to study the use of analgesics in the third trimester of pregnancy which are most common class of drugs prescribed for painful conditions during pregnancy and are the drugs which are used commonly as over the counter drugs by pregnant women. The effects of use of such drugs on pregnancy and outcome of pregnancy was studied. In our study majority of pregnant women were in the age group of 21-25 years (53.6%) followed by those in the age group of 26-30, <20, >30 years constituting 27%, 18.7% and 0.8% respectively. Majority of them were primigravida constituting about 60% of study population.

In a previous study data regarding demographic details of study population showed that 1.8% of study population were in the age group of <20 years followed by 43.6%, 53.4% and 1.2% in the age group of 20-29, 30-39 and > 40 years. About 48.5% were primigravida and 51.5% were multigravida.[10] In our study paracetamol and tramadol were the most commonly used analgesics. Main indication for prescription of tramadol was to relieve false and true labour pain. And indication for use of paracetmol was to treat painful conditions of pregnancy like headache, backache and other types of aches. Majority of analgesics were prescribed by physician and only 6.9% of pregnant used over the counter analgesics to relieve pain. Paracetamol was the most commonly used over the counter drug by pregnant women. In a study from USA, OTC medications like ibuprofen that were contraindicated

during pregnancy were used at higher rates during pregnancy.[11]

Li D et al, conducted a population based cohort study to assess the exposure to non-steroidal anti-inflammatory drugs during pregnancy and risk of miscarriage and found that prenatal use of NSAIDS and aspirin around conception or during pregnancy increased the risk of miscarriage. They also found that prenatal use of paracetamol which is pharmacologically different from other NSAIDS was not associated with increased risk of miscarriage.[12] A populations based observational and case-control study was conducted by Nielsen G et al. to study the adverse birth outcome and miscarriage in pregnant users of NSAIDS. They concluded that use of NSAIDS during pregnancy was not associated with increased risk of adverse outcome like low birth weight, preterm delivery and congenital abnormality but it was associated with increased risk of miscarriage. They also found association between exposure to acetaminophen with preterm birth but it was limited to women with preeclampsia.[13]

In a study conducted by Pour H R N et al on 4705 cases of spontaneous abortion found that use of non-aspirin NSAIDS during pregnancy was significantly associated with risk of spontaneous abortion (odds ratio 2.43, 95% CI: 2.12-2.79). The highest risk was seen among women who used diclofenac alone (OR: 3.09. 95% CI: 1.96-4.87) and low risk was seen among pregnant women who used rofecoxib.[14] A prospective cohort study was conducted by Henriksen KN et al to find the effects of ibuprofen, diclofenac, naproxen and piroxicam on the course of pregnancy and pregnancy outcome it was found that there was no effect of analgesics on rate of infant survival, congenital malformation, or structural heart defects.

Use of ibuprofen in the second trimester was associated with low birth weight (adjusted OR 1.7, CI: 1.3-2.3) and use in the third trimester was associated with asthma in 18 months old children. Use of diclofenac in the second trimester was significantly associated with low birth weight andits use in the third trimester was significantly associated with maternal vaginal bleeding.[10] In our study we found that exposure to analgesics particularly paracetmol was associated with increased risk of preterm delivery and low birth weight with odds ratio of 3.66 and confidence interval of 2.69 - 5 for preterm delivery and OR: 2.52, CI: 1.86-3.37 for low birth weight respectively.

Kristensen D M et al studied the intrauterine exposure to mild analgesics is a risk factor for development of male reproductive disorders in human and rat and found that use of mild analgesics during second trimester was dose-dependently associated with congenital cryptorchidism and risk is more if other analgesics are used together.[15] Similar observation was found in a study conducted by Snijder C A. suggest that intrauterine exposure to mild analgesics, primarily paracetamol, during the period in pregnancy when male sexual differentiation takes place, increases the risk of cryptorchidism.[16]

Our study showed use of analgesics particularly in the 29th and 33rd weeks of gestation was associated with increased risk of preterm delivery and also exposure to analgesics during 29th and 35th weeks of gestation had highest risk of Low birth weight among newborns. In our study none of the pregnant women took over the counter opioid analgesics. Opioids analgesics were prescribed by the obstetricians mainly to treat false labour pain and true labour pain. In a previous study it was concluded that opioid analgesics were prescribed to 21% of pregnant women in their 2nd and 3rd trimester.[15] Neonatal withdrawal has been observed with use of codeine in late pregnancy, even with therapeutic doses in non-addicted mothers.[16,17]

Brandlistuen RE, et al, showed the association between prenatal paracetamol exposure and child's neurodevelopment: a sibling-controlled cohort study concluded that children exposed to long-term use of paracetamol during pregnancy had substantially adverse developmental outcomes at 3 years of age.[18] In a Danish prospective cohort of 64,322 pregnancies, acetaminophen use in pregnancy was associated with significantly higher scores for behavioural problems at 7 Years of age (risk ratio 1.13, 95% CI 1.01 to 1.27).[19] In our study most commonly used analgesics were paracetamol and tramadol. Paracetamol was used mainly to treat painful conditions of pregnancy like headache, backache, fever with myalgia and significant number of pregnant women also used paracetamol as over the counter drugs.

Physicians had the adequate knowledge regarding safety of use of analgesic during pregnancy. Only the paracetamol was prescribed to treat painful event of pregnancy. None of the women self medicated with other NSAIDS, which are considered to be unsafe during pregnancy, this may be due to fear of use of drugs during pregnancy. Tramadol was the only opioid analgesics used to treat false and true labour pain among pregnant women which is considered to be safe opioid during pregnancy and none of the pregnant women self-medicated with opioid analgesics. Adverse drug events like nausea and vomiting was observed in few pregnant women who were prescribed opioid analgesics either to relieve false or true labour pain and was seen in lesser percentage in pregnant women who were exposed to paracetamol, this explains the central actions of opioids to cause nausea and vomiting. None of the patient in this study had severe adverse outcome like APH, PPH due to exposure to analgesics and there were no cases of still birth, birth defects and other major congenital anomalies observed in our study.

CONCLUSION

In this prospective observational study we found that there is an association between the exposure to analgesics during third trimester of pregnancy and preterm delivery and low birth weight. Percentage of preterm deliveries was more among pregnant women who were exposed to paracetamol than those exposed to tramadol during third trimester of

pregnancy in our study. Association between low birth weight and paracetamol exposure was also found. But increased incidence of low birth weight may also be due to preterm deliveries which could not be ruled out in our study. Self-medication of analgesics was found in significant number of pregnant women. Paracetamol was the only analgesic used as over the counter drugs by these study subjects. Tramadol was the most commonly used analgesic to relieve false labour pain and also during true labour pain. Few cases of nausea and vomiting as adverse drug events were found in some of pregnant women who are prescribed tramadol. Other than these adverse events none of the study subjects had severe adverse outcome like APH, PPH and there were no cases of still birth, birth defects and other major congenital anomalies in the neonates of pregnant women exposed to analgesics in this study. Further studies are needed to be done to find the correlation between analgesic usage during third trimester of pregnancy and risk of preterm delivery, since there are only few studies available till now.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee of MIMS, Mandya

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Cite this article as: Sri Vidya BP, Shashikumar NS, Manohar R. Study of analgesics usage in third trimester of pregnancy and its ill effects on pregnancy course and outcome. Int J Basic Clin Pharmacol 2017;6:2282-8.