Original Article

Analgesics and Anti-inflammatory Prescription for Pregnant Women, Military and Khartoum Teaching Hospitals, Khartoum, Sudan, 2016

Azhari E. H. Elamin[1]*; Rasha. M.A.Rifat[2]; Omer.E.H.Elamin[3]; Iman. A. M.Mohamed[4]

[1]Department of Clinical Pharmacy and Pharmacy Practice, Alfajr College for Science and Technology and Khartoum University, Khartoum, Sudan.
[2] Omdurman Islamic University, Khartoum, Sudan.
[3] Sudan Medical Specialization Board, Khartoum Teaching Hospital, Khartoum, Sudan.
[4] Omdurman Islamic University, Khartoum, Sudan.

***Corresponding Author:**
Dr. **Azhari Elnour Haj Elamin**
E mail: azhari_elamin@yahoo.com; azhari_elamin @hotmail.com

Abstract:

Background: Pregnancy loss, preterm delivery and maternal illness are all made more likely by active rheumatic, musculoskeletal, fever, and pain conditions. Pregnant women endure a range of aches and pains, and the majority of them can be treated without the use of analgesics/anti-inflammatory drugs. Many of these drugs are accessible over the counter. Some analgesic treatments may be teratogenic or fetotoxic in pregnancy.

Aim: This study aims to provide information on the analgesics and anti-inflammatory prescription to pregnant women and to correlate the prescriptions to women's characteristics including their medical history, in Khartoum, Sudan.

Methods: The study was a descriptive cross-sectional hospital-based study conducted at the Military and Khartoum Teaching Hospitals in Khartoum State. A data collection form designed by the researcher was used to obtain information on pregnant women from records during the period from January 2015 to January 2016. Women's characteristics, their medical history and the prescriptions for different types of analgesics and anti-inflammatory drugs were extracted. The Chi-square test was used and a p-value < 0.05 was judged statistically significant when analyzing the data using SPSS version 16.

Results:
The records of 650 expectant mothers were reviewed. Analgesic and anti-inflammatory medications were prescribed to 63 (9.7%) of the women. Of those women, 53 (84%) were in their third trimester; *p*=0.0001. Therapeutic agents used were: acetylsalicylic acid (aspirin) used in 39 (61.9%) of this group; followed by dexamethasone in 15 (23.8%); diclofenac sodium in 5 (7.9%), mefnamic acid in 2 (3.2%), and acetaminophen (paracetamol) in 2 (3.2%). The rate of prescription of Analgesic/anti-inflammatory drugs during pregnancy in this study is comparable to international literature. Acetylsalicylic acid (aspirin) was used in low doses (81 – 100 mg). Indications for using low dose aspirin (LDA) in this group were, Systemic hypertension (n=24; 61.5%); venous thromboembolism (n=7; 17.9%); hypertension-during-pregnancy (n=4; 10.2%); diabetic mellitus (n=2; 5.1%) and congenital hyperadrenalism (n=2; 5.1%).

Conclusions: In this study, various analgesics and anti-inflammatory drugs were used to treat minor to moderate pain, headaches and/or fever during pregnancy at a prescription rate comparable to the international literature. Although studies have shown that analgesic and anti-inflammatory medications can be safely taken during pregnancy, they should be under the supervision of qualified physicians and pharmacists for the appropriateness of the treatment and to avoid drug-related problems.

Keywords: *Pregnancy, Analgesic/Anti-inflammatory Drugs, NSAIDs, Acetyl salicylic acid, Low-Dose Aspirin, Acetaminophen, Paracetamol.*

Introduction:

Pregnancy loss, preterm delivery and maternal illness are all more likely made by active rheumatic, musculoskeletal, fever and pain conditions.(1) Many of the aches, pains, and headaches that pregnant women feel don't need analgesic treatment. During pregnancy, headaches and soreness from dental operations are frequent. **(2,3)** With just a few exceptions, the majority of commercially available non-narcotic analgesics (many of which are over-the-counter medicines) can be used safely to relieve minor pregnancy-related pain. **(4,5)**
Some pregnant women may experience headaches often. The best approach is to strike a balance between activity and rest. Although occasionally taking acetaminophen (paracetamol) is safe, it is typically best to avoid medications while pregnant. **(2,3,6)**

Depression and anxiety can develop from continuous pain that is not properly handled. These could have a negative effect on a woman's physical and psychological health as well as her pregnancy. Pain should not be endured by women during pregnancy or nursing. Common analgesics like paracetamol, aspirin, non-steroidal anti-inflammatory drugs (NSAIDs) and opioids are relatively safe when used as directed and appropriately **(7, 8,9)**. Due to lack of information regarding possible risks and benefits, choosing and taking these medicines can be difficult for doctors, pharmacists, and patients.(1) Fortunately, guidelines for the use of anti-rheumatic drugs like NSAIDs in pregnancy and lactation have been published by the American College of Rheumatology, American College of Obstetrics and Gynecology, British Rheumatology Society, and the European League against Rheumatism.
When counseling women about using medications during pregnancy, the physician should always emphasize that all couples have a background risk of about 3% of having a child with a serious birth defect and that 15% of all known pregnancies end in miscarriage, regardless of any drug exposures. (**10,11**)

Over 85% of women in their third trimesters of pregnancy take some form of medication, with analgesics being the most frequently used medicines second only to vitamins. Overall, 50% of women use analgesics during pregnancy. **(10, 11)**
Honest and accurate discussions about pregnancy planning and management are essential to support women in making choices that are in the best interests of their unborn children because many patients are reluctant to use analgesics during pregnancy.(1)
This study aims to provide information on the analgesic and anti-inflammatory prescription rates for expecting mothers who visited the outpatient clinics of the Military and Khartoum Teaching Hospitals between January 2015 and January 2016. This study also aims to find the correlation between the characteristics of the pregnant women and the frequency/rate of prescription of analgesic/anti-inflammatory drugs on participating subjects.

Materials and Methods:
This was a descriptive cross-sectional hospital-based study carried out in the Military and Khartoum Teaching Hospitals in Khartoum State, Sudan, from Jan 2015- Jan 2016. The two hospitals provided Obstetric Care in separate Departments where services were run by house officers, medical officers, registrars, and consultants. The study population included the records of pregnant women attending the two hospitals during the study period. Data collection forms were used to extract the information from pregnant women's files. The information extracted included characteristics of subjects (age, trimester and parity), medical history, maternal disorders and analgesic/anti-inflammatory drugs prescription by type. The sample size was a full coverage to all 650 records of pregnant women attending the outpatient clinics of the two hospitals in the study period.

Data was analyzed using SPSS version 16. Chi square test was the statistical method used. *p value* of <0.05 was considered statically significant.

Results:

The study covered 650 files of pregnant women who attended the outpatient clinics of the two hospitals. The age range of the study population was 15 to 45 years, the majority (67.7%) was multigravidas and 86.6% were in their third trimester (**Table1**)

Table (1): Characteristics of 650 Pregnant Women who attended the Outpatient Clinics of the Military and Khartoum Teaching Hospitals, Khartoum, Sudan

Characteristic	n (%)
Age	
15-25 years	256 (39.4%)
26-35 years	310 (47.7%)
36-45 years	84 (12.9%)
Trimester	
First (1-3 months)	9 (1.4%)
Second (4-6 months)	78 (12.0%)
Third (7-9 months)	563 (86.6%)
Parity	
Primigravida	210 (32.3%)
Multigravida	440 (67.7%)

Maternal Medical Disorders:

One hundred and fifty-four (23.7%) of the pregnant women had maternal medical disorders. In this group, hypertension-during-pregnancy was the most common disorder affecting 14.3%, followed by primary hypertension and urinary tract infections (UTI), in 9.74% each. **(Table 2) shows details of these medical disorders during pregnancy.**

Table (2): Types of Maternal Medical Disorders among 154 Pregnant Women who attended the Outpatient Clinics of the Military and Khartoum Teaching Hospitals, Khartoum, Sudan

Maternal Medical Disorders	n (%)
Hypertension during pregnancy	22 (14.3%)
Systemic Hypertension	15 (9.74%)
UTI*	15 (9.74%)
Pneumonia	11 (7.14%)
Diabetes during pregnancy	11 (7.14%)
Anemia	11 (7.14%)
Others**	69 (44.8%)
Total	154 (100%)
*UTI = urinary tract infections ** Others = sporadic medical problems.	

Prescription of Analgesic and Anti-inflammatory Drugs:
Sixty-three (9.7%) of the 650 pregnant women were prescribed analgesic and anti-inflammatory drugs. In this group, acetylsalicylic acid (aspirin) was the most prescribed drug for 61.9% of patients, followed by dexamethasone for 23.8%. (Table 3) shows details of all the analgesic and anti-inflammatory drugs prescribed.

Table (3): Prescription of Analgesic/Anti-inflammatory Drugs to 63 Pregnant Women attended the Outpatient Clinics of the Military and Khartoum Teaching Hospitals, Khartoum, Sudan

Analgesic/ Anti-inflammatory Drugs	n (%)	
Acetylsalicylic acid (Asprin)	39	(61.9%)
Dexamethasone	15	(23.8%)
Diclofenac sodium	5	(7.9%)
Mefnamic acid	2	(3.2%)
Paracetamol	2	(3.2%)
Total	63	(100 %)

In the third trimester of pregnancy, aspirin was the most frequently prescribed analgesic/anti-inflammatory drug. It was used for various stages of systemic hypertension; followed by venous thromboembolism and hypertension-during-pregnancy (Table 4). Aspirin was used in low doses (81-100 mg/day) as a platelet inhibitor for this group of medical conditions.

Table 4: Use of Acetylsalicylic acid (Aspirin) in low doses for medical conditions during the third trimester in 39 pregnant women

Conditions		n (%)
Systemic Hypertension		24 (61.5%)
Venous Thromboembolism		7 (17.9%)
Hypertension-During-Pregnancy		4 (10.2%)
Diabetic Mellitus		2 (5.1%)
Congenital Hyperadrenalism		2 (5.1%)
Total		39 (100%)

Correlations between the Frequency of Prescription of Analgesic/Anti-inflammatory Drugs; parity and medical history are shown in (Table **5)**. In the 63 pregnant women who were prescribed analgesic/anti-inflammatory drugs during pregnancy, this was highest during the third trimester (84.1%).

Table (5): Correlation between the Characteristics of Pregnant Women and Frequency of Prescription of Analgesic/Anti-inflammatory Drugs among Women attended the Outpatient Clinics of the Military and Khartoum Teaching Hospitals, Khartoum, Sudan.

Item	Analgesic and Anti-inflammatory prescription frequency	*p*- Value
Trimester		0.0001
First (1-3 months)	4	
Second (4-6 months)	6	
Third (7-9 months)	53	
Medical History		0.0001
Hypertension	13	
Asthma	2	
Diabetic	2	
Migraine	2	

Discussion:

In this study, prescription of analgesic/anti-inflammatory drugs increased with pregnancy timing, so that 84.1% of prescriptions were noted during the third trimester.

Asprin was the most frequently prescribed analgesic/**anti-inflammatory** drug during the third trimester of pregnancy. It was used for various stages of systemic hypertension, hypertension-during-pregnancy and venous thromboembolism. The most likely indication was prophylaxes or therapy for various maternal and fetal effects.

Numerous studies have examined the impact of low dose aspirin (LDA) therapy on various maternal and fetal effects. The most recent research findings, published in the year 2021, are included in a summary of the present LDA usage recommendations, along with potential LDA treatment implications for the future.(12)

LDA use appears to be effective in reducing the risk of preeclampsia, preterm birth, and intrauterine growth restriction. However, current research advises raising the recommended dose to >100 mg to maximize these risk reductions. (12) The recent recommendations of reevaluation of using LDA emphasize on dosing and treatment initiation options. When treatment is started before 16 weeks of pregnancy, there is evidence that a decreased incidence of preeclampsia is observed in using aspirin at doses >100 mg.(12) Generally, aspirin is one of the drugs most used by pregnant women. In one prospective study of 1529 pregnant women, almost 50% of the women reported taking aspirin, and about 3% took it daily. High or

normal doses (>325 mg) block the production of prostacyclin and thromboxane, and low-dose aspirin (60–83 mg) results in a selective block of thromboxane production and favors the prostacyclin (vasodilation) pathway **(4,5)**.

A meta-analysis study included a total of 35 placebo-controlled randomized studies with 46,568 pregnant women. Pre-eclampsia, premature delivery, perinatal mortality, and intrauterine growth retardation were all significantly reduced with aspirin prophylaxis without increased bleeding risks. (13) Although LDA did not reduce the chance of gestational hypertension, it significantly increased neonatal birth weight. The subset analysis showed that women who started taking aspirin before 20 weeks of pregnancy had significantly lower pre-eclampsia risk and higher birth weight and gestational age at delivery (RR=0.76, 95% CI=0.64, 0.90, p=0.001). (13)

Among 144 pregnant women who were 'heavy aspirin' users, the frequency of major birth defects in offspring was 4.2% ; not significantly different from that in the general population (3.5–5%).(4) Similarly, among 62 women who used aspirin in the first trimester, the rate was not significantly higher than that expected in the general population.(5) High-dose aspirin taken late in the third trimester may be associated with (a) closure of the ductusarteriosus, (b) persistent pulmonary hypertension, (c) decreased fetal renal function and (d) oligohydramnios. **(4,5).**

Care should be taken of aspirin adverse drug reactions if used by pregnant women; such as gastric irritation and bleeding; hypersensitivity reactions; provoking asthma attacks; urticaria and angioedema. Aspirin is also associated with Reye's syndrome, a rare but potentially fatal encephalopathy of infants and children **(6, 8, 14).** Maternal use of high-dose aspirin is associated with increased frequency of post-term pregnancies, low birth weight, neonatal bleeding disorders, intracranial hemorrhage in premature infants, and premature closure of the ductusarteriosus in the fetus. However, these complications were not associated with aspirin use when pharmacologically controlled doses of salicylates were used. **(4,5,8,15,16)** As long as aspirin daily doses don't surpass 100mg, its use during pregnancy is regarded as safe. In high-risk patients, aspirin has been shown to be effective in preventing pre-eclampsia and fetal development restriction. Neither the prevention of vascular placental disease in low risk individuals nor the benefits of prescribing aspirin in instances of unexplained recurrent miscarriages have been proven.(17)

In this study paracetamol was used during pregnancy, second only to aspirin. In a large longitudinal study, 41% of pregnant women reported paracetamol use during pregnancy.(4) The frequency of congenital birth defects was not increased among more than 1200 offspring of mothers who used paracetamol during the first trimester compared to non-users.

The Intelligence Quotient (IQ) of offspring at 4 years of age whose mothers had ingested paracetamol during pregnancy was no different than controls. **(4,5)**

A summary of available data on the negative effects of long-term paracetamol use, with particular emphasis on cardiovascular disease, asthma, renal injury, and in utero exposure was published by McCrae *et al* in 2018.(18)

In our study, paracetamol was used only to relieve pain and/or fever. Paracetamol is generally safe, its only major drawback being hepatotoxic in overdose. The toxic level of paracetamol need not be greatly above the therapeutic level (4 g daily for adults and children over 12 years) and symptoms of overdose may not appear for two days or more. **(8,13,14)**

Dexamethasone is commonly used in the late second and early third trimesters to promote fetal lung maturity and prevent respiratory distress syndrome.(19) In this study dexamethasone was used in 15 pregnant women (23.8%) which is comparable to other studies in the literature. (20, 21) Glucocorticoids, which include dexamethasone and betamethasone are frequently used to encourage fetal lung maturity and avoid respiratory distress syndrome in the late second and early third trimesters. **(19, 20, 21)** However**,** glucocorticoids are reported to be associated with an increased frequency of cleft palate in the offspring of pregnant animals when used during embryogenesis. Nevertheless, this risk has been estimated to be small in human pregnancy being less than 1%. **(22.23).**

The use of non-steroidal anti-inflammatory drugs (NSAIDs) was small in this study (diclofenac sodium 7.9% and mefnamic acid 3.2%). This was probably reasonable due to their limited use during the second and third trimesters for symptomatic relief,

For low to moderate pain and fever, paracetamol and NSAIDs are both suitable options, but due to known risks, NSAIDs should be avoided during the third trimester. Although neonatal abstinence syndrome must be watched for after exposure in the third trimester, short doses of weaker opioids are typically harmless during pregnancy (24, 25)

Conclusion:

In this study, the use of analgesic and anti-inflammatory drugs in pregnant women was limited to only 9.7% of the study population. Acetylsalicylic acid (aspirin) in low doses was the most frequently prescribed; and mostly during the third trimester (23.8%). The indications for such use were appropriate. The rate of analgesic/anti-inflammatory prescriptions during pregnancy in Sudan is comparable to other relevant literature.

Pregnant and nursing women and their doctors should be reassured that there are safe ways to manage pain, both acute and chronic. Occasional

analgesic/anti-inflammatory drugs can be taken during pregnancy; but it should be prescribed carefully by physicians and checked by pharmacists for the appropriateness of the treatment and to avoid drug-related problems.

Funding:

Authors own resources

Conflict of interest

None

References:

1. Mehret BTalabi, Megan E B Clowse. Antirheumatic medications in pregnancy and breastfeeding. CurrOpinRheumatol. 2020 May;32(3):238-246.
2. Neumann, P. J., Sanders, G. D., Russell, L. B., Siegel, J. E., &Ganiats, T. G. (Eds.). (2016).Clinical study and Cost-effectiveness in health and medicine. Oxford University Press.
3. Joseph, T., DiPiro, R., Robert, L. Talbert , G, C., Yee , G., Matzke , W. B. , L. Michael, P.(2008). Pharmacotherapy- A Pathophysiologic Approach (Pharmacotherapy), 7th edition. McGraw-Hill Medical Posey Press, New York.
4. Little.B. Bertis (2006). Drugs and pregnancy hand book, *Analgesics during pregnancy*, Oxford University, New York, chapter 8, *pp 149-163.*
5. Little.B. Bertis (2006). Drugs and pregnancy hand book, *Adrenocorticosteroids*, Oxford University, New York, chapter 13, *pp 247*
6. British National Formulary (BNF) (2010). Joint Formulary Committee. British Medical Association and Royal Pharmaceutical Society of Great Britain. BNF # BMJ Group and RPS Publishing. Pharmaceutical Press, London, Vol.59.
7. Symptoms in the Pharmacy: A Guide to the Management of Common Illness, 6th Edition Alison Blenkinsopp, P. Paxton and J. Blenkinsopp © 2009. ISBN: 978-1-405-18079-5.
8. Drug Information: A Guide for Pharmacists, 4rd Edition (2016). Patrick M. Malone, Karen L. Kier, John E. Stanovich.
9. Fick, D. M., Cooper, J. W., Wade, W. E., Waller, J. L., Maclean, J. R., & Beers, M. H. (2003). Updating the Beers criteria for potentially inappropriate medication use in older adults: results of a US consensus panel of experts. Archives of internal medicine, 163(22), 2716-2724.
10. Henry A, Crowther C. (2000). Patterns of medication use during andprior to pregnancy: the MAP study. Aust NZ J ObstetGynaecol; 40:165-72.
11. Fick, D. (2001). Potentially inappropriate medication use in a Medicare managed care population: association with higher costs and utilization. Journal of Managed Care Pharmacy, 7(5), 407-413.

12. Andrew R Mather, Aaron M Dom, Loralei L Thorburg .Low-dose aspirin in pregnancy: who? when? how much? and why?. Review CurrOpinObstet Gynecol. 2021;33(2):65-71.
13. Yeo Jin Choi, Sooyoung Shin. Aspirin Prophylaxis during Pregnancy: A Systematic Review and Meta-Analysis. Review Am J PrevMed. 2021;61(1):31-34
14. Alomar, M. J. (2014). Factors affecting the development of adverse drug reactions. Saudi pharmaceutical journal, 22(2), 83-94.
15. Shepard TH, Brent RL, Friedman JM, Jones KL, Miller RK, Moore CA, Polifka JE. Update on new developments in the study of human teratogens. Teratology. 2002;65(4):153-61.
16. Kimble, M .K., , . Young .L.Y ,Kradjan .W. A. et al. Applied Therapeutics. The Clinical Use of Drugs. 9th edition .Lippincott Williams & Wilkins Press, US.
17. N Belhomme 1 , C Doudnikoff 2 , E Polard 3 , B Henriot 4 , H Isly 5 , P Jego 6 . Aspirin: Indications and use during pregnancy .Review Rev Med Interne. 2017;38(12):825-832.
18. J C McCrae 1 , E E Morrison 1 , I M MacIntyre 1 , J W Dear 1 , D J Webb 1. Long-term adverse effects of paracetamol - a review .Review Br J ClinPharmacol. 2018;84(10):2218-2230
19. 19 Brunton, L . Chabner, B. A, Knollman, B (2011). Goodman and Gilman's (The Pharmacological Basis of Therapeutics). 12Edition: McGraw-Hill Medical Press -New York.; 12 edition (1 Feb 2011). Teratology; 65: 153.
20. Johnson, PD, Dawson BV, Goldberg, SJ.(1998) Cardiac teratogenicity of trichloroethylene
21. metabolites. J Am CollCardiol; 32: 540.
22. WHO: Model List of Essential Medicines (2011).Available: http://www.whqlibdoc.who.int/. Accessed 31 Dec 2013.
23. Whaley R J, Fletcher KE, Weston SE, Howard RL and Rawlinson CF (2008) .Foundation in pharmacy practice Oxford:Oxford: university press.
24. Chumney, E. C., & Robinson, L. C. (2006). The effects of pharmacist interventions on patients with polypharmacy. Pharmacy Practice, 4(3), 103-109.
25. Eleanor Black 1 2 , KokEngKhor 3 4 , Debra Kennedy 5 6 , AnuntaponChutatape 7 , Swapnil Sharma 3 8 , Thierry Vancaillie 6 9 , Apo Demirkol. Medication Use and Pain Management in Pregnancy: A Critical Systematic Review and Meta-analysis .Review Pain Practice. 2019;19(8):875-899.
26. N Belhomme 1 , C Doudnikoff 2 , E Polard 3 , B Henriot 4 , H Isly 5 , P Jego 6 . Aspirin: Indications and use during pregnancy .Review Rev Med Interne. 2017;38(12):825-832.
27. Xiuhua Yang, YingyingTian, LinlinZheng, ThanhLuu, Joanne Kwak-Kim. The Update Immune-Regulatory Role of Pro-and Anti-Inflammatory Cytokinases in Recurrent Pregnancy Losses. Review Int J MolSci, 2022; 24(1):132.