

RISING CAESAREAN SECTIONS: A Call For Evaluation Of Dosing in Pre-Operative Drugs at a tertiary care hospital

Dr. Divya S Nair
Assistant Professor
Aditya College of Pharmacy

Dr. Padala Srilakshmi
Duty Medical Officer
Medicover Hospital, Kakinada

Dr. Annapoorna Yalla
Head of the Department

Department of Obstetrics and Gynaecology, GSL general hospital, Rajanagaram, Andhra Pradesh, India

ABSTRACT:

Aim: To evaluate pre-operative drug dosing and discuss various purpose and complications of caesarean sections at a tertiary care hospital. **Objectives:** To determine sub use or overuse of pre-operative drugs, To create awareness of the increasing risk of complications which followed increase in rate of voluntary caesarean sections without complications. **Materials and methods:** In our study dose evaluation was done by comparing the average prescribing dose with World Health Organisation Defined Daily Dose. Qualitative analysis was performed to understand various purpose and complications of caesarean sections. **Results:** It was found that 41.94% of patients had no complications to undergo caesarean sections. The most common post complications of caesarean section was found to be anemia (7.53%) and infections (7.53%). It was also found that cefotaxime was being sub-used (Prescribed Daily Dose/Defined Daily Dose=0.25) though there is no evidence of teratogenicity whereas diclofenac was over-used (Prescribed Daily Dose/Defined Daily Dose=1.50) in spite of possibility of teratogenic effects. **Conclusion:** Teratogenicity Vs efficacy evaluation based on dosing could be suggested for the caesarean section procedure.

INTRODUCTION:

The accelerating count of the number of cesarean section taking place globally, proportionally increases the risk of developing complications¹. The purpose of cesarean section is to save the life of the baby and the mother in cases of complications or in cases where vaginally delivery is not possible². But in the current scenario the patients voluntarily prefer cesarean considering their comfort even though they have no complications. This study also creates awareness of the complications that might occur following the procedure, therefore aids in decision making by such patients. Pre-operative drugs used in C section is one of the key factors that determines the effectiveness of the procedure. Hence, it calls for an attention towards dosing and patient's physiology. Pregnancy involves several physiological changes such as increase in plasma volume, decrease in binding proteins, changes in metabolizing enzymes, decreased gastrointestinal motility, changes in Glomerular Filtration Rate etc., these changes can cause failure of drug action or lead to toxic effects³. Therefore it is necessary to evaluate the drug doses in order to obtain drug effectiveness.

METHODOLOGY:

A sample size of 93 was taken and a prospective study was performed. The study included pregnant women who underwent cesarean section at a tertiary care hospital. Data was collected using patient profile forms and the patient's complications, comorbidities, and pre-operative drugs and their dosage regimens were recorded. The study involved assessment of complications and comorbidities that led to Caesarean section, and post Caesarean section complications along with assessment of dosage regimens of drugs that were used pre-operatively. A comparison between the standard average doses (WHO DDD) and the prescribed average doses (PDD) of the pre-operative drugs was performed to see if the drugs are being overused ($PDD/DDD > 1$) or subused ($PDD/DDD < 1$). Therefore the drugs which do not have WHO DDD available were excluded. The data was analysed for the above objectives using JMP® Pro version 16.0.0 (SAS institute Inc.) and Microsoft® Excel® 2016 MSO (Version 2204).

RESULTS and DISSCUSSION:

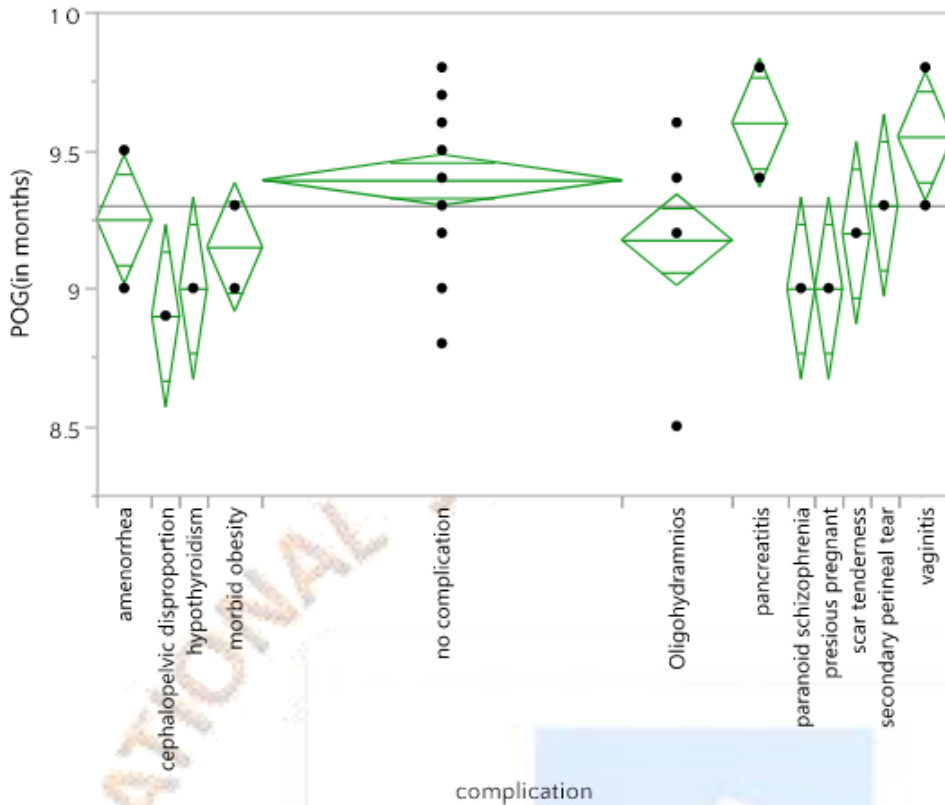


Figure 1: Period of gestation based on complications that led to caesarean section

One way ANOVA for Period Of Gestation was performed in the study population which shows F distribution ($p=0.0012$) significant at 0.05 level of significance. Considering the means of POG, pre-term deliveries mostly occurred among patients with cephalopelvic disproportion (8.90 months), hypothyroidism(9.00 months), morbid obesity (9.15 months), oligohydroamnios (9.17 months), paranoid schizophrenia (9.00 months), previous pregnant (9.00 months) and scar tenderness (9.20 months).

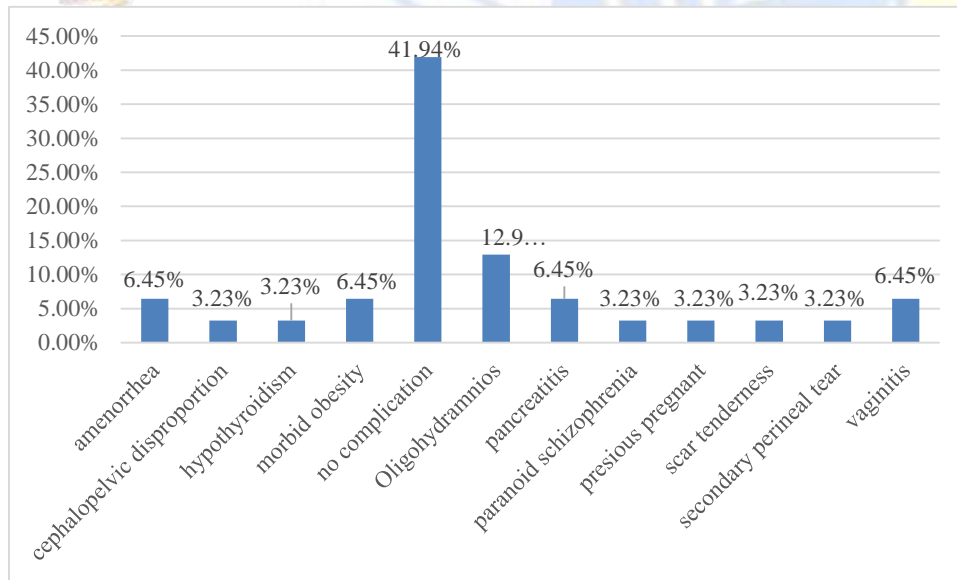


Figure 2: Complications based on number of patients

Most patients preferred Caesarean section though they did not have any complications in their pregnancy (figure 2). Such decision could lie on both medical and non-medical reasons. Medical reason could involve prolonged labour but in our population all patient’s POG was below 10 months, whereas the non-medical reasons could involve other factors like fear and second thoughts about vaginal birth. Superstitious beliefs can also be a contributing factor here as some communities believe in giving birth as their presumed auspicious time and date.

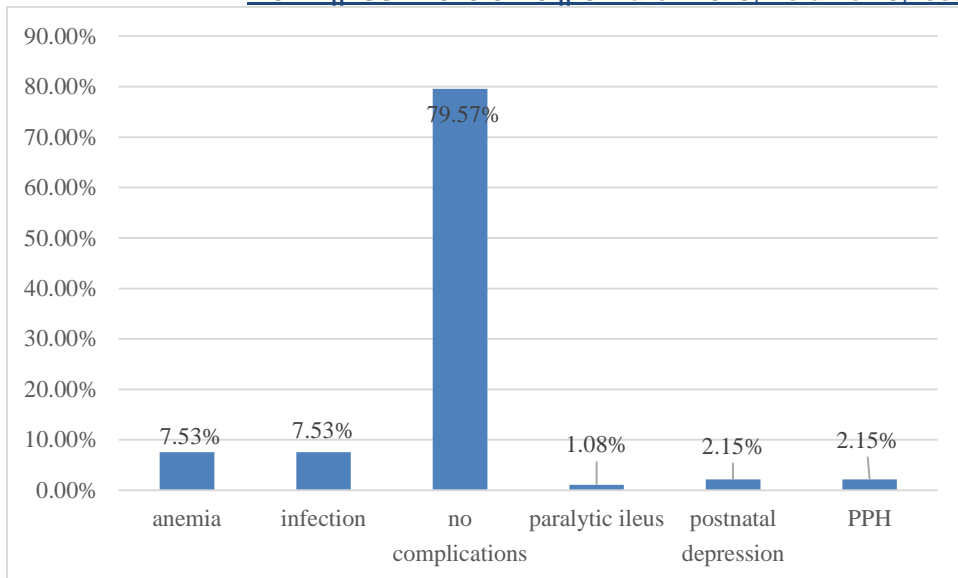


Figure 3: Post caesarean section complications based on number of patients

As per the figure 3, the most occurring complications were anemia and infections. Anemia is one of the common complications that occur post Caesarean section and has to be monitored closely for medication adherence towards taking prophylactic iron supplements during the entire gestation period⁴. Anemia can also occur due to post partum hemorrhage as it involves blood loss >500ml which is most commonly managed by a hysterectomy. Infections post Caesarean section can be either an SSI or any other infection. Such occurrence of infections can be avoided by providing the adequate dosage regimen especially when there are recurrent history of bacterial infections. Post partum depression can occur in both vaginal delivery and Caesarean section and is usually associated with an unplanned cesarean delivery.

| Dosage form | Antibiotics | ATC Code | PDD | DDD | PDD/DDD | Drug utilization | Significant association of drug with teratogenicity |
|-------------|----------------|----------|------|------|---------|------------------|--|
| parenteral | cefotaxim | J01DD01 | 1000 | 4000 | 0.25 | subuse | Not found ⁵ |
| | pantoprazole | A02BC02 | 40 | 40 | 1.00 | optimal | Not found ⁶ |
| | Ondansetron | A04AA01 | 4 | 16 | 0.25 | subuse | Not found ⁷ |
| | gentamycin | J01GB03 | 80 | 240 | 0.33 | subuse | Requires more evidence ⁸ |
| | ceftriaxone | J01DD04 | 1000 | 2000 | 0.50 | subuse | Possible on frequent use ⁹ |
| | ranitidine | A02BA02 | 150 | 300 | 0.50 | subuse | Not found ¹⁰ |
| | h.actrapid | A10AB01 | 0.14 | 5.6 | 0.025 | subuse | Requires more evidence ¹¹ |
| | ampicillin | J01CA01 | 2000 | 6000 | 0.33 | subuse | No evidence for pre-operative use ¹² |
| | amikacin | J01GB06 | 500 | 1000 | 0.50 | subuse | Found on zebrafish ¹³ |
| | metoclopramide | A03FA01 | 10 | 30 | 0.33 | subuse | No evidence for pre-operative use ¹⁴ |
| | diclofenac | M02AA15 | 150 | 100 | 1.50 | overuse | Possible on frequent use ¹⁵ |
| | metronidazole | J01XD01 | 1500 | 1500 | 1.00 | optimal | Not found ¹⁶ |
| oral | metformin | A10BD23 | 520 | 2000 | 0.26 | subuse | Possible (based on animal models) ¹⁷ |
| oral | levetiracetam | N03AX14 | 500 | 1500 | 0.33 | subuse | Possible (No evidence for pre-operative use) ¹⁸ |

Table 1: Drug utilization evaluation based on PDD/DDD and Teratogenic evidence of those drugs

Based on the listed pre-operative drugs (Table 1), it is observed that, most drugs are being sub-used than the average maintenance doses. Cefotaxim was subused though no evidence of teratogenicity is observed in any of the previous studies. This study population showed 7.53% of patients with post Caesarean section infection, such patients who are prone to infection can receive cefotaxim with an increase in dosage regimen (upto 4000mg/day) to prevent infection efficiently. Diclofenac was being overused in this study population, but the drug can cause embryotoxicity on frequent use. Pre-operative use of gentamycin, ceftriaxone, human insulin, ampicillin, metoclopramide, metronidazole, metformin and levetiracetam are required to be studied in a larger population for teratogenic effects. Therefore, such drugs must be carefully considered for their possible teratogenic effects prior use as pre-operative prescription.

CONCLUSION:

Cesarean section is a lifesaving and cost-effective intervention when performed safely using evidence-based practices. Therefore, as clinical pharmacist we suggest that, healthcare providers should advice to avoid c section when there is no complications affecting the mother or the fetus. It is also essential that the prescribers consider all possible evidences of teratogenicity and efficacy for the dose of drugs being prescribed.

REFERENCES:

- 1) WHO founded in 1948 - caesarean-section-rates-continue-to-rise-amid-growing-inequalities-in-access 16 June 2021(departmental news).
- 2) Zakerihamidi M, Latifnejad Roudsari R, Merghati Khoei E. Vaginal Delivery vs. Cesarean Section: A Focused Ethnographic Study of Women's Perceptions in The North of Iran. *Int J Community Based Nurs Midwifery*. 2015 Jan;3(1):39-50.
- 3) Ke AB, Greupink R, Abduljalil K. Drug Dosing in Pregnant Women: Challenges and Opportunities in Using Physiologically Based Pharmacokinetic Modeling and Simulations. *CPT Pharmacometrics Syst Pharmacol*. 2018 Feb;7(2):103-110.
- 4) Kalaivani, K. "Prevalence & consequences of anaemia in pregnancy." *Indian J Med Res* 130.5 (2009): 627-33. Rai RK, Fawzi WW, Barik A, Chowdhury A. The burden of iron-deficiency anaemia among women in India: how have iron and folic acid interventions fared?. *WHO South-East Asia J Public Health* 2018;7:18-23. Kamau, Mary Wanjira, Waithira Mirie, and Samuel Kimani. "Compliance with Iron and folic acid supplementation (IFAS) and associated factors among pregnant women: results from a cross-sectional study in Kiambu County, Kenya." *BMC public health* 18.1 (2018): 1-10.
- 5) Dimitris A. Kafetzis, Cosmas V. Lazarides, Constantinos A. Sifas, Panagiotis A. Georgakopoulos, Constantinos J. Papadatos, Transfer of cefotaxime in human milk and from mother to foetus, *Journal of Antimicrobial Chemotherapy*, Volume 6, Issue suppl_A, 1980, Pages 135–141.
- 6) Cheng Mei Li, Alexandra Zhernakova, Lars Engstrand, Cisca Wijmenga, Nele Brusselaers, Systematic review with meta-analysis: the risks of proton pump inhibitors during pregnancy, *Alimentary Pharmacology & Therapeutics*, 10.1111/apt.15610, 51, 4, (410-420), (2020).
- 7) Bengt Danielsson, Birgitta Norstedt Wikner, Bengt Källén, Use of ondansetron during pregnancy and congenital malformations in the infant, *Reproductive Toxicology*, Volume 50, 2014, Pages 134-137, ISSN 0890-6238,
- 8) Nahum, Gerard G., Kathleen Uhl, and Dianne L. Kennedy. "Antibiotic use in pregnancy and lactation: what is and is not known about teratogenic and toxic risks." *Obstetrics & Gynecology* 107.5 (2006): 1120-1138.
- 9) Erić, Mirela, and Ana Sabo. "Teratogenicity of antibacterial agents." *Collegium antropologicum* 32.3 (2008): 919-925.
- 10) Ruigómez, Ana, et al. "Use of cimetidine, omeprazole, and ranitidine in pregnant women and pregnancy outcomes." *American journal of epidemiology* 150.5 (1999): 476-481.
- 11) Lo, W. Y., and J. M. Friedman. "Teratogenicity of recently introduced medications in human pregnancy." *Obstetrics & Gynecology* 100.3 (2002): 465-473. H. actrapid (short acting)
Lambert, K., and R. I. G. Holt. "The use of insulin analogues in pregnancy." *Diabetes, obesity and metabolism* 15.10 (2013): 888-900.
- 12) Czeizel, Andrew E., et al. "A population-based case-control teratologic study of ampicillin treatment during pregnancy." *American journal of obstetrics and gynecology* 185.1 (2001): 140-147.
- 13) Chen, Ying-Hsin, et al. "Fin reduction is a novel and unexpected teratogenic effect of amikacin-treated zebrafish embryos." *Toxicology Mechanisms and Methods* 22.2 (2012): 151-158.
- 14) Berkovitch, Matitahu, et al. "Metoclopramide for nausea and vomiting of pregnancy: a prospective multicenter international study." *American journal of perinatology* 19.06 (2002): 311-316.
- 15) Chae, Jeong-Pil, et al. "Evaluation of developmental toxicity and teratogenicity of diclofenac using *Xenopus* embryos." *Chemosphere* 120 (2015): 52-58.
- 16) Pascale Burtin, Anna Taddio, Omer Ariburnu, Thomas R. Einarson, Gideon Koren, Safety of metronidazole in pregnancy: A meta-analysis, *American Journal of Obstetrics and Gynecology*, Volume 172, Issue 2, Part 1, 1995, Pages 525-529, ISSN 0002-9378.
- 17) Brock, Birgitte, et al. "Is metformin therapy for polycystic ovary syndrome safe during pregnancy?." *Basic & clinical pharmacology & toxicology* 96.6 (2005): 410-412.
- 18) Vajda, F. J. E., et al. "The teratogenicity of the newer antiepileptic drugs—an update." *Acta Neurologica Scandinavica* 130.4 (2014): 234-238.

- 19) Gyamfi-Bannerman, Cynthia, et al. "Antenatal betamethasone for women at risk for late preterm delivery." *New England Journal of Medicine* 374.14 (2016): 1311-1320.
- 20) Gharehbaghi K1, Gharehbaghi DR2, Wierrani F2, Sliutz G2 *Zeitschrift fur Geburtshilfe und Neonatologie*, [Treatment of Chronic Functional Constipation during Pregnancy and Lactation]. 11 Feb 2016, 220(1):9-15 Language:ger
- 21) Fujinaga, Masahiko, Joseph B. Stevenson, and Richard I. Mazze. "Reproductive and teratogenic effects of fentanyl in Sprague-Dawley rats." *Teratology* 34.1 (1986): 51-57.
- 22) Suwanrath, C., Chunuan, S., Matemanosak, P. et al. Why do pregnant women prefer cesarean birth? A qualitative study in a tertiary care center in Southern Thailand. *BMC Pregnancy Childbirth* 21, 23 (2021).
- 23) Fenwick, Jennifer, et al. "Why do women request caesarean section in a normal, healthy first pregnancy?." *Midwifery* 26.4 (2010): 394-400.

