DOI: 10.7860/JCDR/2021/49372.15103

Original Article

Obstetrics and Gynaecology Section

Single vs Multiple Antibiotic Drug Regimen in Preventing Infectious Morbidity in Caesarean Section: A Randomised Clinical Trial

SUBHASHCHANDRA R MUDANUR[1], SHREEDEVI S KORI[2], ARUNA BIRADAR[3], RAJASRI G YALIWAL[4], DAYANAND S BIRADAR[5], SANTOSH RAMDURG[6], SINDHU MANNE[7]

BY-NC-ND

ABSTRACT

Introduction: Surgical site infections are a serious cause of maternal morbidity and mortality. Various preventive measures are being used to reduce the incidence of surgical site infections. One of them is the use of prophylactic antibiotics. In this study, authors have evaluated three antibiotic regimen with respect to preventing infectious morbidity in caesarean section.

Aim: To study the efficacy and cost-effectiveness of a single dose (ceftriaxone) versus multiple doses of antibiotic therapy (ceftriaxone and ornidazole) administered preoperatively in women undergoing caesarean delivery.

Materials and Methods: A prospective interventional study was conducted on 300 pregnant women undergoing emergency or elective caesarean delivery. Study was conducted at BLDE (DU) Shri BM Patil Medical College and Research Centre, Vijayapur, Karnataka, India. Patients were randomly assigned to three groups by block random sampling with 100 women in each group. Group A received Inj. ceftriaxone 1gm single dose 60 minutes prior to commencement of surgery. Group B received Inj. ceftriaxone 1gm along with Inj. ornidazole 500mg intravenous infusion 60 minutes prior to commencement of surgery and Group C received Inj. ceftriaxone 1gm and Inj. ornidazole 500mg intravenous infusion 60 minutes prior to commencement of surgery and a repeat dose 12th hourly for 24 hours followed by Tab. cefixime 200mg and Tab. ornidazole 500mg twice a day for four days postoperatively. The effectiveness of therapy was measured in terms of adverse effects of antibiotics such as nausea and vomiting and postoperative complications like pyrexia, foul smelling lochia, surgical site infections, uterine tenderness, peritonitis and endometritis.

Results: There was no statistical difference in outcome measures in side-effects of antibiotics (p=0.13), fever (p=0.68), lochia discharge (p=0.88), wound infection (p=0.39) and peritonitis (p=0.30) among the three groups. The single dose medication in group A had a cost of Rs.60 INR (0.82 cents USD), which was significantly less compared to the multiple dose regimens in group B that cost Rs.203 INR ($2.76 USD). The mean hospital stay in non-infectious and infectious patients were 5 and 10 days in present study (p<0.0001).

Conclusion: Caesarean delivery poses 5-20 times greater risk of postoperative infection when compared to vaginal birth. There has been a shifting trend of increasing caesarean deliveries and postoperative infections can contribute to overwhelming health and economic burden. Present study shows outcome measures which were statistically insignificant among the three study groups with different prophylactic regimen for caesarean delivery, so it's safe to state that both single dose and multiple dose regimen provided equal protective coverage in reducing maternal infectious morbidity. Also, single dose regimen proved to be cost-effective. So, to conclude single dose prophylactic antibiotic given preoperatively in caesarean section is both cost-effective and as is efficient.

Keywords: Antibiotics in pregnancy, Caesarean delivery, Ceftriaxone, Ornidazole

INTRODUCTION

Antisepsis principles was first introduced by Joseph Lister in 1860 which demonstrated marked decrease in incidence of postoperative infection. Later in 1960, Burke demonstrated on animal models that use of prophylactic antibiotics before surgical procedure can decrease the rate of wound contamination [1]. Postoperative infections following surgical procedures in obstetric patients are a significant source of maternal morbidity and mortality. Caesarean deliveries are known to cause 5-20 times increased risk of infections in women compared to vaginal birth [2]. Cochrane library suggested the use of prophylactic antibiotic course in women undergoing caesarean delivery after evidence suggested reduction in rate of wound infection by 30-65% and a decrease in endometritis by 60-70% [2]. Preoperative antibiotic coverage has been proven to be favourable in reducing infectious morbidity and hospital stay [3-6].

The overall rate of caesarean sections worldwide has been on the rise. Initially, the rate was 21.1 of all births in 2015 with a steady increase at an annual rate of 3.7% between the years 2000-2015. Specifically, in South Asian countries the rate of caesarean sections has doubled between 2000-2015 with an annual rate of 5%. The rate of caesarean section has reached 18.1% in 2015 that exceeds the 15% of all deliveries recommended by World Health Organisation (WHO) upper limit of caesarean section rate [7]. So, a sepsis and prophylactic antibiotics in caesarean delivery are mainstay of management in reducing maternal infectious morbidity and mortality.

To date, several antibiotics have been suggested to be effective when used alone or in combination for prophylactic coverage in obstetric patients undergoing caesarean section. Traditionally, in caesarean section, prophylactic antibiotic use is given in a single dose regimen. However, the inconsistency of use has warranted the need for an extensive literature review [8]. An ideal prophylactic regimen should have clinically proven efficacy, broad spectrum coverage against infective organisms, be inexpensive, well tolerated and should not develop antibiotic resistance [9-11]. In recent times, injudicious use of antibiotics has added to financial burden, high

incidence of resistance and suboptimal treatments and this calls for a standard regimen to be devised to reduce antibiotic misuse, avoid patient discomfort and undesirable side-effects ranging for mild nausea to severe drug reactions.

In view of the current needs, high efficacy and cost-effective prophylactic measures are required and keeping that in mind, this study was designed to compare the effectiveness of single dose of antibiotic regimen versus multiple drugs and the cost involved. This study aims to provide a simple yet important answer as to which is better and how cost is factored into the treatment and outcome.

MATERIALS AND METHODS

This randomised clinical trial study was carried out in BLDE (DU) Shri BM Patil Medical College Hospital and Research Centre in Vijayapura, Karnataka State, India. BLDE(DU) Shri BM Patil Medical College and Research Center is 1200 bedded tertiary care centre attached to BLDE University which is well known in Northern Karnataka. It was conducted from 28thOctober, 2018 to 4th February, 2020. The Ethical Clearance for the study was obtained from the Institutes Ethical Committee BLDE (Deemed to be University), Vijayapura, Karnataka State, India (IEC/304/2018-19).

Inclusion criteria: The study included consenting pregnant women above 28 weeks of gestation admitted to the hospital undergoing elective or emergency caesarean delivery for singleton pregnancy. Participants were unblinded to the procedure.

Exclusion criteria: Patients having Premature Rupture Of Membranes (PROM), blood loss of more than 1000mL, prolonged and obstructed labour, intraoperative complications such as bowel and bladder injury and those requiring peripartum hysterectomy were excluded.

Sample size: If no difference between standard and experimental treatment was found and to be 80% sure (study power) that the limits of two sided 90% confidence interval will exclude a difference between standard and experimental group of more than 20%, then sample size was estimated as 300 patients with 100 patients in each group. Sample was calculated using the formula,

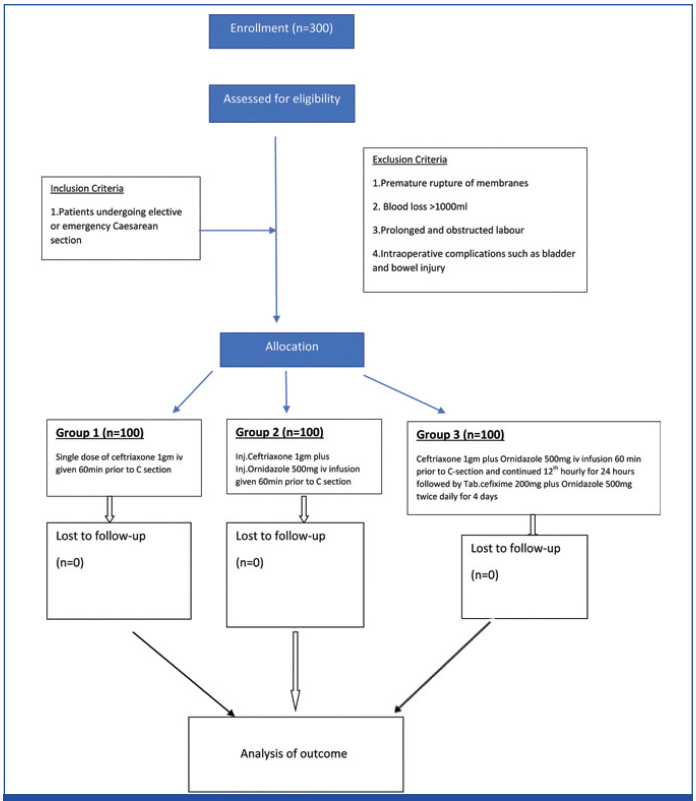
$n=2 \times f(\alpha, \beta/2) \times \pi \times (100-\pi)/d^2$. Where, f is distribution function, α value is level of significance, β is power of study, π is the true percent 'success' in both control and experimental treatment groups and d is margin of error. There were no drop outs or cross over between the groups.

Study involved three groups. Group A received Inj. ceftriaxone 1gm single dose 60 minutes prior to commencement of surgery. Group B received Inj. ceftriaxone 1gm along with Inj. ornidazole 500mg intravenous infusion 60 minutes prior to commencement of surgery and Group C received Inj. ceftriaxone 1gm and Inj. ornidazole 500mg intravenous infusion 60 minutes prior to commencement of surgery and a repeat dose 12th hourly for 24 hours followed by Tab. cefixime 200mg and Tab. ornidazole 500mg twice a day for four days postoperatively.

Primary outcome measured were postoperative infectious morbidity which includes fever, wound infection, peritonitis, endometritis, lochia discharge and uterine tenderness. Adverse effects of antibiotic such as nausea and vomiting were considered secondary outcome. Cost incurred with different regimen was also analysed to estimate the cost-effectiveness in association with treatment efficacy. [Table/Fig-1] denotes the algorithm for patient's participation and enrollment of the study population. There are various treatment guidelines for antimicrobial use in common syndromes, Indian Council of Medical Research, Department of Health Research, New Delhi, India 2017 [12].

Procedure

Computer generated block randomisation was done and the study participants were allocated to three different groups with clearly



[Table/Fig-1]: Enrollment of study population.

defined prophylactic regimen which was different for each group. All caesarean sections were done under spinal anaesthesia. All caesareans were done by consultant obstetricians. Prior to surgery, the abdomen was painted with povidone-iodine solution followed by surgical spirit. The uterus was closed in single layer with continuous interlocking suture using polyglactin 910 and skin was closed with monofilament Nylon 2-0 with mattress sutures. Strict aseptic measures were followed and minimal intra and postoperative handling was done. Patients were allowed to mobilise 12 hours postsurgery and urinary catheters was removed after mobilisation.

Sutures were removed on postoperative day eight and patients were followed-up on postoperative day 15. Patients with no complications were discharged in eight days and those who presented infective wound were discharged on day 15. All patients at discharge were advised regarding wound care, nutrition and hygiene and were asked to report in case of any symptoms of infection such as fever, nausea or pain and discharge at surgical site.

STATISTICAL ANALYSIS

Statistical data calculations were done using Statistical Package for the Social Science (SPSS Inc., Version 20.0, Chicago, IL, USA) and described in terms of mean, median, frequencies, interquartile range and number of cases in percentages for continuous variables and Chi-square test was done for categorical data. The p-value <0.05 was considered significant.

RESULTS

[Table/Fig-2] shows baseline characteristics of study participants among the three groups such as age, full term or preterm delivery, presence or absence of PROM, presence of pregnancy induced hypertension, gestational diabetes and gravida were homogenous (p >0.05), however, there was difference in number of women undergoing elective and non-elective caesarean section between the study groups (p <0.001).

No statistical difference was observed in outcome parameters among the study groups i.e., side-effects of antibiotics or postoperative complications such as postoperative fever (p=0.689), foul smelling lochia discharge (p=0.881), wound infection (p=0.394), peritonitis (p=0.308). No cases of uterine tenderness or endometritis were reported in any group [Table/Fig-3].

Variables	Group A		Group B		Group C		χ^2 value	p-value
	N	%	N	%	N	%		
Age (years)								
≤25	69	69.0	61	61.0	67	67.0	1.538	0.464
>25	31	31.0	39	39.0	33	33.0		
Preterm/Term								
Preterm	18	18.0	8	8.0	16	16.0	4.651	0.098
Term	82	82.0	92	92.0	84	84.0		
PROM								
No	82	82.0	78	78.0	79	79.0	0.535	0.765
Yes	18	18.0	22	22.0	21	21.0		
Gravida								
Primi	34	34.0	33	33.0	31	31.0	0.212	0.899
Multi	66	66.0	67	67.0	69	69.0		
Co-morbidities								
PIH	34	34.0	32	32.0	32	32.0	0.142	0.971
GDM	34	34.0	32	32.0	32	32.0	0.142	0.971
LSCS								
Emergency	80	80.0	14	14.0	81	81.0	1.86	<0.001*
Elective	20	20.0	86	86.0	19	19.0		

[Table/Fig-2]: Distribution of baseline characteristics in study participants.
*p-value highly significant; PROM-Premature rupture of membranes; PIH-Pregnancy induced hypertension; GDM-Gestational Diabetes Mellitus; LSCS-Lower section cesarean section

Variables	Group A		Group B		Group C		χ^2 value	p-value
	N	%	N	%	N	%		
Side-effects of antibiotics								
Nausea	3	3.0	1	1.0	0	0.0	7.11	0.13
Vomiting	1	1.0	3	3.0	0	0.0		
Postoperative complications								
Post Op fever	5	5.0	3	3.0	7	7.0	2.254	0.689
Lochia discharge	5	5.0	7	7.0	6	6.0	1.182	0.881
Wound infection	7	7.0	10	10.0	5	5.0	1.86	0.394
Uterine tenderness	0	0.0	0	0.0	0	0.0	-	-
Peritonitis	1	1.0	1	1.0	1	1.0	4.807	0.308
Endometritis	0	0.0	0	0.0	0	0.0	-	-

[Table/Fig-3]: Postoperative infectious morbidity among study participants.

Cost of Medications: Inj. ceftriaxone 1gm received by group A participants cost Rs.60 INR (0.82 cents USD). Prophylactic regimen of group B included Inj.Ceftriaxone 1gm and Inj. ornidazole 500mg single dose and this combination costed Rs.203 INR ($2.76 USD). Group C medications costed Rs.894 INR ($12.15 USD) for combination of medications which were ceftriaxone 1 gm plus ornidazole 500 mg iv for 24 hours followed by Tab.cefixime 200 mg plus ornidazole 500 mg twice daily for four days. Comparing the cost involved among three regimens, it's quite evident that multiple drug regimen was approximately 15 times more expensive that single dose regimen. Mean hospital stay in non-infectious and infectious patients were 5 and 10 days in present study (p<0.0001).

DISCUSSION

Postoperative wound infection and dehiscence is an impending issue for the operating surgeon. The increasing incidence of wound dehiscence has marred the advancement in surgical techniques and availability of surgery. Several internal factors such as diabetes, hypertension and wound infection, suturing practices, suture material and wound care like external factors can affect the complex process of wound healing. The incidence of infection in postcaesarean wound infection and independent risk factors related with it has been studied retrospectively [13].

Preoperative short course prophylactic antibiotic coverage before obstetric procedure such as caesarean section is known to reduce incidence of endometritis and wound infection and has also proved to be cost-effective due to decrease in patient morbidity and duration of hospital stay [14]. Cochrane Database of Systemic Reviews were meta-analysed by Smaill F and Hofmeyr GJ for the role of antibiotic prophylaxis in caesarean section and they reported the effectiveness of preoperative antibiotic coverage for reducing maternal morbidity and mortality [15]. Hopkins L and Smaill F in the Cochrane review evaluated several multicentre trials, different antibiotics used for prophylaxis based on the route of administration and the number of doses and concluded that the benefits incurred from single or multiple dose regimen were similar and posed no added benefits [16]. A single vs multiple dose antibiotic given preoperatively provide similar benefits in terms of decreasing postoperative infectious morbidity [17-20]. Similar results were demonstrated from present study where three different regimen provided similar benefit to the patient on postoperative complications.

Tchabo JG et al., study presented no significant difference in occurrence of wound infection and duration of hospital stay due to variability in single vs multiple dose regimen which mirrors the data of present study [21]. This study addressed the cost analysis of each regimen among the three groups and showed the difference the price incurred.

Most commonly occurring postoperative infectious morbidities are febrile morbidity, surgical site infection and urinary infection. Infectious morbidity leads to prolonged hospital stay and treatment cost. Incidence of febrile morbidities were found to be 5%, 6.5% and 6.5% [22-24]. Following caesarean delivery, the incidence range of surgical site infection is 3-15% with a mean of 6% [25,26]. The results from present study showed surgical site infection in 5-10% cases across study groups post prophylactic medications. Urinary tract infections commonly occur postoperatively due to frequent catheterisation, multiple per vaginal examination, asepsis during any interventional procedure and occult bacteraemia. The incidence UTI in past studies such as Shakya K and McMurray C and William N et al., was found to be 3.5 and 2%, respectively [22,26]. Infectious morbidity can prolong hospital stay and associated psychological distress in patients. Mean hospital stay in non-infectious and infectious patients were 5 and 10 days in present study while Ziogos E et al., noted average of four days' hospital stay. In developing countries like India and Nepal, the patients are supposed the bear the medical expenses so cost involved during hospital stay was of utmost concern [27]. Kayihura V et al., concluded that single dose prophylactic regimen costs one tenth of cost incurred from multiple dose regimen, similarly present study noted that multiple dose regimen costed 15 times more than single dose regimen [28].

Limitation(s)

Neonatal outcomes were not studied and patients did not come for in follow-up visits. Long term studies with larger sample size are needed.

CONCLUSION(S)

Multiple drug dose does not provide added benefits when compared to single drug dose. Single drug prophylaxis costs significantly less than multiple drug regimen and are equally effective in reducing complications and hospital stay.

Acknowledgement

Authors would like to acknowledge Mr. Mohd Shahnawaz MSc statistics for his continuous help in drafting the statistics. I would like to thank my parents, my family and my children for their constant support for my research work.

REFERENCES

[1] Burke JF. The effective period of preventive antibiotic action in experimental incisions and dermal lesions. Surgery. 1961;50:161-68.
[2] Smaill FM, Gyte GM. Antibiotic prophylaxis versus no prophylaxis for preventing infection after caesarean section. Cochrane Database Syst Rev. 2010;(1):CD007482. Update in: Cochrane Database Syst Rev. 2014;10:CD007482.

[3] Killian CA, Graffunder EM, Vinciguerra TJ, Venezia RA. Risk factors for surgical-site infections following caesarean section. Infect Control Hosp Epidemiol. 2001;22(10):613-17.
[4] Gibbs RS, DeCherney AH, Schwarz RH. Prophylactic antibiotics in caesarean section: A double-blind study. Am J Obstet Gynecol. 1972;114(8):1048-53.
[5] Harger JH, English DH. Selection of patients for antibiotic prophylaxis in caesarean sections. Am J Obstet Gynecol. 1981;141(7):752-58.
[6] Duff P, Smith PN, Keiser JF. Antibiotic prophylaxis in low-risk caesarean section. J Reprod Med. 1982;27(3):133-38.
[7] World Health Organization. WHO Statement on Caesarean Section Rates. Geneva, Switzerland: Department of Reproductive Health and Research, World Health Organization; October, 2018.
[8] Pinto-Lopes R, Sousa-Pinto B, Azevedo LF. Single dose versus multiple dose of antibiotic prophylaxis in caesarean section: A systematic review and meta-analysis. BJOG. 2017;124(4):595-605.
[9] Cartwright PS, Pittaway DE, Jones HW 3rd, Entman SS. The use of prophylactic antibiotics in obstetrics and gynecology. A review. Obstet Gynecol Surv. 1984;39(9):537-54.
[10] Carey B, Cryan B. Antibiotic misuse in the community--A contributor to resistance? Ir Med J. 2003;96(2):43-44, 46.
[11] Klem C, Dasta JF. Efforts of pharmacy to reduce antibiotic resistance. New Horiz. 1996;4(3):377-84.
[12] Indian Council of Medical Research. Treatment Guidelines for Antimicrobial Use in Common Syndromes. New Delhi: ICMR; 2017. [accessed on January 31, 2018]. Available from: http://iamrsn.icmr.org.in/images/pdf/STG270217.pdf
[13] Metgud MC, Kataria A, Nadipally SR, Patil K. Incidence of wound dehiscence following obstetric and gynecological surgeries at a tertiary care hospital: A retrospective study. J South Asian Feder Obst Gynae. (2020);12(2):73-78.
[14] ACOG educational bulletin. Antimicrobial therapy for obstetric patients. Number 245, March 1998 (replaces no. 117, June 1988). American College of Obstetricians and Gynecologists. Int J Gynaecol Obstet. 1998;61(3):299-308.
[15] Smaill F, Hofmeyr GJ. Antibiotic prophylaxis for caesarean section. Cochrane Database Syst Rev. 2002;(3):CD000933. Update in: Cochrane Database Syst Rev. 2010;(1):CD000933.
[16] Hopkins L, Smaill F. Antibiotic prophylaxis regimens and drugs for caesarean section. Cochrane Database Syst Rev. 2000;(2):CD001136. Update in: Cochrane Database Syst Rev. 2012;1:CD001136.
[17] Hawrylyshyn PA, Bernstein P, Papsin FR. Short-term antibiotic prophylaxis in high-risk patients following caesarean section. Am J Obstet Gynecol. 1983;145(3):285-89.
[18] Jakobi P, Weissman A, Zimmer EZ, Paldi E. Single-dose cefazolin prophylaxis for caesarean section. Am J Obstet Gynecol. 1988;158(5):1049-52.
[19] McGregor JA, French JI, Makowski E. Single-dose cefotetan versus multidose cefoxitin for prophylaxis in caesarean section in high-risk patients. Am J Obstet Gynecol. 1986;154(4):955-60.
[20] Saltzman DH, Eron LJ, Tuomala RE, Protomastro LJ, Sites JG. Single-dose antibiotic prophylaxis in high-risk patients undergoing caesarean section. A comparative trial. J Reprod Med. 1986;31(8):709-12.
[21] Tchabo JG, Cutting ME, Butler C. Prophylactic antibiotics in patients undergoing total vaginal or abdominal hysterectomy. Int Surg. 1985;70(4):349-52. PMID: 3914473.
[22] Shakya K, McMurray C. Neonatal mortality and maternal health care in Nepal: Searching for patterns of association. J Biosoc Sci. 2001;33(1):87-105.
[23] Alekwe LO, Kuti O, Orji EO, Ogunniyi SO. Comparison of ceftriaxone versus triple drug regimen in the prevention of caesarean section infectious morbidities, J. Matern.-Fetal Neonatal Med. 2008;21(9):638-42.
[24] Ahmed J, Kumar A, Parikh K, Anwar A, Knoll BM, Puccio C, et al. Use of broad-spectrum antibiotics impacts outcome in patients treated with immune checkpoint inhibitors. Oncoimmunology. 2018;7(11):e1507670.
[25] Bagga RS, Shetty AP, Sharma V, Vijayanand KSS, Kanna RM, Rajasekaran S. Does preventive care bundle have an impact on surgical site infections following spine surgery? An analysis of 9607 patients. Spine Deform. 2020;8(4):677-84.
[26] Williams N, Sweetland H, Goyal S, Ivins N, Leaper DJ. Randomised trial of antimicrobial-coated sutures to prevent surgical site infection after breast cancer surgery. Surg Infect (Larchmt). 2011;12(6):469-74.
[27] Ziogos E, Tsiodras S, Matalliotakis I, Giamarellou H, Kanellakopoulou K. Ampicillin/sulbactam versus cefuroxime as antimicrobial prophylaxis for caesarean delivery: A randomised study. BMC Infect Dis. 2010;10:341.
[28] Kayihura V, Osman NB, Bugalho A, Bergström S. Choice of antibiotics for infection prophylaxis in emergency caesarean sections in low-income countries: A cost-benefit study in Mozambique. Acta Obstet Gynecol Scand. 2003;82(7):636-41.

PARTICULARS OF CONTRIBUTORS:
1. Head, Department of Obstetrics and Gynaecology, BLDE University Bijapur, Karnataka, India.
2. Associate Professor, Department of Obstetrics and Gynaecology, BLDE University, Bijapur, Karnataka, India.
3. Associate Professor, Department of Obstetrics and Gynaecology, BLDE University, Bijapur, Karnataka, India.
4. Associate Professor, Department of Obstetrics and Gynaecology, BLDE University, Bijapur, Karnataka, India.
5. Associate Professor, Department of General Surgery, BLDE University, Bijapur, Karnataka, India.
6. Associate Professor, Department of Psychiatry, BLDE University, Bijapur, Karnataka, India.
7. Postgraduate Student, Department of Obstetrics and Gynaecology, BLDE University Bijapur, Karnataka, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Shreedevi S Kori,
Associate Professor, Department of Obstetrics and Gynaecology, BLDE University, Solapur Rd, Bangaramma Sajjan Campus, Bijapur-586103, Karnataka, India.
E-mail: sr.mudanur@bldedu.ac.in

PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Mar 13, 2021
- Manual Googling: May 07, 2021
- iThenticate Software: Jun 30, 2021 (19%)

ETYMOLOGY: Author Origin

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Mar 09, 2021**
Date of Peer Review: **Apr 03, 2021**
Date of Acceptance: **May 07, 2021**
Date of Publishing: **Jul 01, 2021**