Indian Journal of Obstetrics and Gynecology

(A PEER-REVIEWED AND REFEREED JOURNAL)

VOLUME 12 NUMBER 2 APRIL - JUNE 2024

RED FLOWER PUBLICATIONS PVT LTD
New Delhi - 110091

Revised Rates for 2024 (Institutional) **Title of the Journal**	**Frequency**	**India(INR) Print Only**	**India(INR) Online Only**	**Outside India(USD) Print Only**	**Outside India(USD) Online Only**
Community and Public Health Nursing	Triannual	6500	6000	507.81	468.75
Indian Journal of Agriculture Business	Semiannual	6500	6000	507.81	468.75
Indian Journal of Anatomy	Quarterly	9500	9000	742.19	703.13
Indian Journal of Ancient Medicine and Yoga	Quarterly	9000	8500	703.13	664.06
Indian Journal of Anesthesia and Analgesia	Bi-monthly	8500	8000	664.06	625
Indian Journal of Biology	Semiannual	6500	6000	507.81	468.75
Indian Journal of Cancer Education and Research	Semiannual	10000	9500	781.25	742.19
Indian Journal of Communicable Diseases	Semiannual	9500	9000	742.19	703.13
Indian Journal of Dental Education	Quarterly	6500	6000	507.81	468.75
Indian Journal of Diabetes and Endocrinology	Semiannual	9000	8500	703.13	664.06
Indian Journal of Emergency Medicine	Quarterly	13500	13000	1054.69	1015.63
Indian Journal of Forensic Medicine and Pathology	Quarterly	17000	16500	1328.13	1289.06
Indian Journal of Forensic Odontology	Semiannual	6500	6000	507.81	468.75
Indian Journal of Genetics and Molecular Research	Semiannual	8000	7500	625	585.94
Indian Journal of Law and Human Behavior	Semiannual	7000	6500	546.88	507.81
Indian Journal of Legal Medicine	Semiannual	9500	9000	742.19	703.13
Indian Journal of Library and Information Science	Triannual	10500	10000	820.31	781.25
Indian Journal of Maternal-Fetal & Neonatal Medicine	Semiannual	10500	10000	820.31	781.25
Indian Journal of Medical and Health Sciences	Semiannual	8000	7500	625	585.94
Indian Journal of Obstetrics and Gynecology	Quarterly	10500	10000	820.31	781.25
Indian Journal of Pathology: Research and Practice	Triannual	13000	12500	1015.63	976.56
Indian Journal of Plant and Soil	Semiannual	7500	7000	585.94	546.88
Indian Journal of Preventive Medicine	Semiannual	8000	7500	625	585.94
Indian Journal of Research in Anthropology	Semiannual	13500	13000	1054.69	1015.63
Indian Journal of Surgical Nursing	Triannual	6500	6000	507.81	468.75
Indian Journal of Trauma and Emergency Pediatrics	Quarterly	10500	10000	820.31	781.25
Indian Journal of Waste Management	Semiannual	10500	10000	820.31	781.25
International Journal of Food, Nutrition & Dietetics	Triannual	6500	6000	507.81	468.75
International Journal of Forensic Science	Semiannual	11000	10500	859.38	820.31
International Journal of Neurology and Neurosurgery	Quarterly	11500	11000	898.44	859.68
International Journal of Pediatric Nursing	Triannual	6500	6000	507.81	468.75
International Journal of Political Science	Semiannual	7000	6500	546.88	507.81
International Journal of Practical Nursing	Triannual	6500	6000	507.81	468.75
International Physiology	Triannual	8500	8000	664.06	625
Journal of Aeronautical Dentistry	Quarterly	8000	7500	625	585.94
Journal of Animal Feed Science and Technology	Semiannual	9000	8500	703.13	664.06
Journal of Cardiovascular Medicine and Surgery	Quarterly	11000	10500	859.38	820.31
Journal of Emergency and Trauma Nursing	Semiannual	6500	6000	507.81	468.75
Journal of Food Additives and Contaminants	Semiannual	6500	6000	507.81	468.75
Journal of Food Technology and Engineering	Semiannual	6000	5500	468.75	429.69
Journal of Forensic Chemistry and Toxicology	Semiannual	10500	10000	820.31	781.25
Journal of Global Medical Education and Research	Semiannual	7000	6500	546.88	507.81
Journal of Global Public Health	Semiannual	13000	12500	1015.63	976.56
Journal of Microbiology and Related Research	Semiannual	9500	9000	742.19	703.13
Journal of Nurse Midwifery and Maternal Health	Triannual	6500	6000	507.81	468.75
Journal of Orthopedic Education	Triannual	6500	6000	507.81	468.75
Journal of Pharmaceutical and Medicinal Chemistry	Semiannual	17500	17000	1367.19	1328.13
Journal of Plastic Surgery and Transplantation	Semiannual	27500	27000	2148.44	2109.38
Journal of Psychiatric Nursing	Triannual	6500	6000	507.81	468.75
Journal of Radiology	Semiannual	9000	8500	703.13	664.06
Journal of Social Welfare and Management	Quarterly	8500	8000	664.06	625
New Indian Journal of Surgery	Quarterly	9000	8500	703.13	664.06
Ophthalmology and Allied Sciences	Triannual	7000	6500	546.88	507.81
Pediatrics Education and Research	Quarterly	8500	8000	664.06	625
Physiotherapy and Occupational Therapy Journal	Quarterly	10000	9500	781.25	742.19
RFP Gastroenterology International	Semiannual	7000	6500	546.88	507.81
RFP Indian Journal of Hospital Infection	Semiannual	13500	13000	1054.69	1015.63
RFP Indian Journal of Medical Psychiatry	Semiannual	9000	8500	703.13	664.06
RFP Journal of Biochemistry and Biophysics	Semiannual	8000	7500	625	585.94
RFP Journal of Dermatology	Semiannual	6500	6000	507.81	468.75
RFP Journal of ENT and Allied Sciences	Semiannual	6500	6000	507.81	468.75
RFP Journal of Gerontology and Geriatric Nursing	Semiannual	6500	6000	507.81	468.75
RFP Journal of Hospital Administration	Semiannual	8000	7500	625	585.94
Urology, Nephrology and Andrology International	Semiannual	8500	8000	664.06	625

Terms of Supply:

1. Agency discount 12.5%. Issues will be sent directly to the end user, otherwise foreign rates will be charged.
2. All back volumes of all journals are available at current rates.
3. All journals are available free online with print order within the subscription period.
4. All legal disputes subject to Delhi jurisdiction.
5. Cancellations are not accepted orders once processed.
6. Demand draft/cheque should be issued in favour of "**Red Flower Publication Pvt. Ltd.**" payable at **Delhi.**
7. Full pre-payment is required. It can be done through online (http://rfppl.co.in/subscribe.php?mid=7).
8. No claims will be entertained if not reported within 6 months of the publishing date.
9. Orders and payments are to be sent to our office address as given below.
10. Postage & Handling is included in the subscription rates.
11. Subscription period is accepted on calendar year basis (i.e. Jan to Dec). However orders may be placed any time throughout the year.

Order from

Red Flower Publication Pvt. Ltd., 48/41-42, DSIDC, Pocket-II, Mayur Vihar Phase-I, Delhi - 110 091 (India)
Mobile: 8130750089, Phone: 91-11-79695648 E-mail: sales@rfppl.co.in, Website: www.rfppl.co.in

Indian Journal of Obstetrics and Gynecology

RED FLOWER PUBLICATION PVT. LTD.

Managing Editor

A. Lal

Publication Editor

Dinesh Kr. Kashyap

Indian Journal of Obstetrics and Gynecology (IJOG) (pISSN: 2321–1636; eISSN: 2455-5339) publish original, peer-reviewed work in all areas of obstetrics and gynecology, including Obstetrics, Midwifery, Maternal medicine, Fetal medicine, Gynecological urology, Gynecological oncology, Gynecological endocrinology, Infertility, Reproductive medicine, Genitourinary medicine, Sexual medicine, Prenatal diagnosis, Perinatology, Cytopathology, General gynecology, Community gynecology, Family planning, Epidemiology, Reproductive ethics, Research into medical education, Menopause, Operative gynecology. The journal publish original study, reviews, case reports, letters to Editor, short communication, journals scan, conference calendars in all issues.

Readership: Obstetricians, Gynecologists, pediatricians, and neonatologists.

Subscription rates worldwide: Individuals (annual) - Contact us; Institutional (annual, Print+Online)-INR 10500/USD 820.31. Payment methods: By Demand Draft/cheque should be in the name of **Red Flower Publication Pvt. Ltd.** payable at Delhi. By online: http://rfppl.co.in/subscribe.php?mid=7, Bank Transfer/TT: **Bank name:** Bank of India, **IFSC Code:** BKID0006043, **Swift Code:** BKIDINBBDOS, **Account Name:** Red Flower Publication Pvt. Ltd., **Account Number:** 604320110000467, Branch: Mayur Vihar Phase-I, Delhi – 110 091 (India) or you can log on to www.rfppl.co.in.

Printed at Saujanya Printing Press, B-303, Okhla Industrial Area, Phase-1, New Delhi - 110 020.

Red Flower Publication (P) Ltd.

Presents its Book Publications for sale

1. **Beyond Medicine: A to E for Medical Professionals) (2020)**
   Kalidas Chavan
   INR390/USD31
2. **Biostatistical Methods For Medical Research (2019)**
   Sanjeev Sarmukaddam **INR549/USD44**
3. **Breast Cancer: Biology, Prevention And Treatment (2015)**
   Dr. A. Ramesh Rao **INR 395/USD31**
4. **Chhotanagpur A Hinterland of Tribes (2020)**
   Ambrish Gautam **INR250/ USD20**
5. **Child Intelligence (2004)**
   Dr. Rajesh Shukla, Md, Dch. **INR100/ USD50**
6. **Clinical Applied Physiology and Solutions (2020)**
   Varun Malhotra **INR263/USD21**
7. **Comprehensive Medical Pharmacology (2019)**
   Dr. Ahmad Najmi **INR599/USD47**
8. **Critical Care Nursing in Emergency Toxicology (2019)**
   Vivekanshu Verma **INR460/USD34**
9. **Digital Payment (Blue Print For Shining India) (2020)**
   Dr. Bishnu Prasad Patro **INR329/USD26**
10. **Drugs in Anesthesia (2020)**
    R. Varaprasad **INR449/USD35**
11. **Drugs In Anesthesia and Critical Care (2020)**
    Dr. Bhavna Gupta **INR595/USD46**
12. **MCQs in Medical Physiology (2019)**
    Dr. Bharati Mehta **INR300/ USD29**
13. **MCQs in Microbiology, Biotechnology and Genetics (2020)**
    Biswajit Batabyal **INR285/USD22**
14. **MCQs In Minimal Access and Bariatric Surgery (2nd Edition) (2020)**
    Anshuman Kaushal **INR545/USD42**
15. **Patient Care Management (2019)**
    A.K. Mohiuddin **INR999/USD78**
16. **Pediatrics Companion (2001)**
    Rajesh Shukla **INR 250/USD50**
17. **Pharmaceutics-1 (A Comprehensive Hand Book) (2021)**
    V. Sandhiya **INR525/ USD50**
18. **Poultry Eggs of India (2020)**
    Prafulla K. Mohanty **INR390/USD30**
19. **Practical Emergency Trauma Toxicology Cases Workbook (2019)**
    Dr. Vivekanshu Verma, Dr. Shiv Rattan Kochar, Dr. Devendra Richhariya **INR395/USD31**
20. **Practical Record Book of Forensic Medicine & Toxicology (2019)**
    Dr. Akhilesh K. Pathak **INR299/USD23**
21. **Recent Advances in Neonatology (2020)**
    Dr. T.M. Ananda Kesavan **INR 845/USD66**
22. **Shipping Economics (2018)**
    Dr. D. Amutha **INR347/USD45**
23. **Skeletal and Structural Organizations of Human Body (2019)**
    Dr. D.R. Singh **INR659/USD51**
24. **Statistics In Genetic Data Analysis (2020)**
    S.Venkatasubramanian **INR299/USD23**
25. **Synopsis of Anesthesia (2019)**
    Dr. Lalit Gupta **INR1195/USD75**
26. **A Handbook of Outline of Plastic Surgery Exit Examination (2022)**
    Prof Ravi Kumar Chittoria & Dr. Saurabh Gupta **INR 498/USD 38**
27. **An Introductory Approach to Human Physiology (2021)**
    Satyajit Tripathy, Barsha Dasssarma, Motlalpula Gibert Matsabisa **INR 599/USD 46**
28. **Biochemical and Pharmacological Variations in Venomous Secretion of Toad (Bufo melanostictus)(2021)**
    Dr. Thirupathi Koila & Dr. Venkaiah Yanamala **INR 325/USD26**
29. **Climate, Prey & Predator Insect Poupulation in Bt Cotton and Non-Bt Cotton Agriculture Feilds of Warangal District (2022)**
    Dr. Peesari Laxman,Ch. Sammaiah **INR 325/USD26**
30. **Community Health Nursing Record Book Volume – I & II (2022)**
    Ritika Rocque **INR 999/USD 79**
31. **Handbook of Forest Terminologies (Volume I & II) (2022)**
    Dr. C.N.Hari Prasath, Dr. A. Balasubramanian, Dr. M. Sivaprakash, V. Manimaran, Dr. G. Swathiga **INR 1325/USD 104**
32. **MCQs of Biochemistry(2022)**
    Sachin C. Narwadiya, Dr. Irfana Begum **INR 399/USD 49**
33. **Newborn Care in the State of Uttar Pradesh(2022)**
    Dr. Tridibesh Tripathy **INR 545/USD 42**
34. **Osteoporosis: Weak Bone Disease(2022)**
    Dr. Dondeti Uday Kumar & Dr. R. B. Uppin **INR 399/USD49**
35. **Quick Updates in Anesthesia(2022)**
    Dr. Rupinder Kaur Kaiche, Dr. Vidhyadhar Modak, Dr. Shilpa Sannakki & Dr. Vivek Gupta **INR 599/USD 44**
36. **Textbook of Practice of Medicine with Homoeopathic Therapeutics(2022)**
    Dr. Pramod Kumar **INR 1325/USD104**
37. **Trends in Anthropological Research(2022)**
    Dr. Jyoti Ratan Ghosh,Dr. Rangya Gachui **INR 399/USD 49**

Order from: Red Flower Publication Pvt. Ltd., 48/41-42, DSIDC, Pocket-II, Mayur Vihar Phase-I, Delhi - 110 091(India), Mobile: 8130750089, Phone: 91-11-79695648, E-mail: info@rfppl.co.in, Website: www.rfppl.co.in

Indian Journal of Obstetrics and Gynecology

April – June 2024
Volume 12 Number 2

Contents

SUBSCRIPTION FORM

I want to renew/subscribe international class journal "**Indian Journal of Obstetrics and Gynecology**" of Red Flower Publication Pvt. Ltd.

Subscription Rates:
- Institutional: INR 10500/USD 820.31

Name and complete address (in capitals):_____

_____

Payment detail:
Online payment link: http://rfppl.co.in/payment.php?mid=15

Cheque/DD: Please send the US dollar check from outside India and INR check from India made payable to 'Red Flower Publication Private Limited'. Drawn on Delhi branch.

Wire transfer/NEFT/RTGS:
Complete Bank Account No. 604320110000467
Beneficiary Name: Red Flower Publication Pvt. Ltd.
Bank & Branch Name: Bank of India; Mayur Vihar
MICR Code: 110013045
Branch Code: 6043
IFSC Code: BKID0006043 (used for RTGS and NEFT transactions)
Swift Code: BKIDINBBDOS

Term and condition for supply of journals
1. Advance payment required by Demand Draft payable to **Red Flower Publication Pvt. Ltd**. payable at **Delhi.**
2. Cancellation not allowed except for duplicate payment.
3. Agents allowed 12.5% discount.
4. Claim must be made within six months from issue date.

Mail all orders to
Subscription and Marketing Manager
Red Flower Publication Pvt. Ltd.
48/41-42, DSIDC, Pocket-II
Mayur Vihar Phase-I
Delhi - 110 091(India)
Phone: 91-11-79695648
Cell: +91-9821671871
E-mail: sales@rfppl.co.in

Editorial

Indian Journal of Obstetrics and Gynecology
Volume 12 Number 2, April – June 2024
DOI: http://dx.doi.org/10.21088/ijog.2321.1636.12224.1

Gestational Trophoblastic Disease: Know the Unbeknown

Nutan Agarwal

Gestational Trophoblastic Disease (GTD) is an unique disorder of fetal tumour in maternal tissue. Diagnosis of this wide spectrum condition is frequently delayed due to its unusual presentations. We usually follow all old described criterias, here are some of my observations based on my clinical based experience which can be considered in future now.

One has to be more vigilant to diagnose partial mole. Ruling out of partial mole should be essential in certain cases, specially diagnosed as missed abortions. One should suspect partial mole in following situations

1. If patient is having persistent nausea or vomiting even in failed early pregnancy.
2. There are increasing βhCG levels despite USG showing missed abortion.
3. Proper USG should be done in all cases of missed abortion.
4. Histopathlogy should be obtained in all cases of missed abortions So that required βhCG follow up can be performed for timely diagnosis of Gestational trophoblastic neoplasia.
5. If Medical methods are used for termination, patient can be guided to be vigilant for expulsion of products and collect them in saline bottle which can be provided before, where microarray can be tested on these products.

Points to ponder: More than 60 cases of GTD were observed where I found 8 cases of partial mole out of 8,1 developed locally invasive disease and 2 Metastatic. Hence I reached on following conclusion.

1. Partial mole incidence may be more than reported. One has to be more vigilant to diagnose.
   a. Any missed abortion, if nausea vomiting, suspect this condition.
   b. Always do βhCG levels in missed abortion.
   c. Always get histopathology of these cases.
2. Partial mole may cause more metastatic disease than reported as they are likely to be missed and later cases of metastatic GTD may be falsely anticipated following antecedent abortion.
3. Partial mole also should be evaluated thoroughly and followed up properly with βhCG levels, It should not be underestimated.
4. Large multicentric trials are required to establish the facts about partial mole.

How to cite this article:

Nutan Agarwal. Gestational Trophoblastic Disease: Know the unbeknown. Indian J Obstet Gynecol. 2024;12(2).

Original Article

Indian Journal of Obstetrics and Gynecology
Volume 12 Number 2, April – June 2024
DOI: http://dx.doi.org/10.21088/ijog.2321.1636.12224.2

Assessment of Applebaum Scoring in Endometrial Evaluation in Prediction of Implantation in Patients with Recurrent Pregnancy Loss

Kiran Pandey[1], Pavika Lal[2], Aishwina Anand[3], Garima Gupta[4], ShailyAgarwal[5]

How to cite this article:
Kiran Pandey, Pavika Lal, Aishwina Anand *et al.* Assessment of Applebaum Scoring in Endometrial Evaluation in Prediction of Implantation in Patients with Recurrent Pregnancy Loss. Indian J Obstet Gynecol. 2024;12(2):57-62.

Abstract

Background: Unexplained recurrent pregnancy loss (RPL) still poses a diagnostic and therapeutic challenge which can be quite distressing to the couples as well as to the gynaecologist. We aimed to study the prevalence of RPL at our tertiary care centre and to assess the efficacy of Applebaum scoring of endometrium for prediction of implantation in cases of unexplained RPL.

Materials and Methods: The study enrolled 43 cases with history of unexplained RPL in non pregnant state and their endometrial evaluation was done with TVS and colour Doppler. 37 patients were taken as controls which were comparable in terms of socio-demographic factors in the age group of 18-35 years. TVS was done on 12th day of menstrual cycle.

Results: The incidence of RPL at our center was found to be 3.68%. It was seen that pregnancy loss was more when endometrial thickness was <7mm or >14 mm. RPL was more when pulsatility index of uterine artery was >2.5 (p=0.004) which was statistically significant as compared to controls. It was observed that when total score was <13, the sensitivity and specificity of predicting implantation was 90.70% and 81.08% respectively.

Conclusion: Applebaum scoring system can be a good predictor in patients with recurrent pregnancy loss especially when no cause has been identified, accordingly therapeutic intervention can be directed to increase endometrial thickness, its vascularity as well as its receptivity.

Keywords: Applebaum Scoring; Endometrial Receptivity; Recurrent Pregnancy Loss.

Author's Affiliation: [1,2]Senior Resident, Department of Obstetrics and Gynecology, Ganesh Shankar Vidyarthi Memorial Medical College, Kanpur 208002, [3,4,5]Senior Resident, Department of Obstetrics and Gynecology, Moti Lal Nehru Medical College, Prayagraj 211002, Uttar Pradesh, India.

Corresponding Author: Aishwina Anand, Senior Resident, Department of Obstetrics and Gynecology, Moti Lal Nehru Medical College, Prayagraj 211002, Uttar Pradesh, India.

E-mail: Aishwina.anand@gmail.com

Received on: 23.05.2024

Accepted on: 03.07.2024

INTRODUCTION

RPL is a complex entity to resolve as its etiopathogenesis is still unclear involving a multifactorial mechanism including immunologic and genetic causes. Moreover, the criteria or diagnosis of RPL involve a lot of controversies as different societies opine differently. According to European Society for Human Reproduction and Embryology and the Royal College of Obstetricians and Gynaecologists, RPL refers to 2 or more consecutive miscarriages.[1] However, according to the American Society for Reproductive Medicine (ASRM), it is defined as two or more clinical pregnancy losses (documented by ultrasonography or histopathologic examination), but not necessarily

consecutive.[2] The incidence varies extensively (0.5-2.3%) because of variation in criteria used as well as the heterogeneity of population. Primary RPL refers to multiple losses in a woman with no previous viable infants, whereas secondary RPL refers to multiple losses in a woman who has already had a pregnancy beyond 20 gestational weeks[3]. RPL can be attributed to innumerable causes but still majority are unexplained or idiopathic.

For a pregnancy to continue till period of viability, process of implantation becomes a critical step for which endometrium undergoes a lot of physiological and immunological changes.[4,5,6]

To evaluate such changes, the role of TVS coupled with Doppler cannot be underestimated due to its easy availability, accessibility and cost effectiveness. Various researchers have evaluated ultrasonographic parameters and scoring systems to predict in infertility patients and one such scoring is applebaum scoring which has only been evaluated in infertile patients and there are very few studies in which endometrium has been evaluated in case of recurrent pregnancy loss. We attempt to undertake this study so as to determine the role of Applebaum scoring in prediction of implantation in patients with unexplained recurrent pregnancy loss.

MATERIALS AND METHOD

The study was conducted in the department of obstetrics and gynaecology along with radiology department at GSVM medical college, Kanpur from January 2020 to October 2021 in patients who came to our out patient department with history of unexplained recurrent pregnancy loss.

Inclusion Criteria: Group 1: Cases included patients with RPL between 18-35 years of age having >/= 2 consecutive or non consecutive pregnancy loss in non pregnant state.

Group 2: Controls included patients between 18-35 years of age in non pregnant state in whom history of RPL (primary or secondary), abnormal uterine bleeding and infertility were excluded.

Exclusion Criteria: Patients having endocrinological abnormalities like hypo/ hyperthyroidism, diabetes mellitus, polycystic ovarian syndrome, inherited thrombophilias like anti-phospholipid antibody syndrome, uterine abnormalities like septate or bicornuate uterus, cervical incompetence. Enrolled patients evaluated by a thorough history, examination and following investigationswere done like S. TSH, Oral glucose tolerance test with 75g glucose, Lupus anticoagulant, anti cardiolipin antibody, Beta 2 glycoprotein 1. Patients were evaluated with transvaginal ultrasonography along with colour Doppler on day 12 of menses using LOGIQP9 machine with 4-9 MHz probe. Patients were asked to lie down in lithotomy position after emptying the bladder. Maximum thickness of endometrium was measured from zona basalis of anterior wall of endometrial cavity till zona basalis of posterior wall and was designated as distinct 5 line appearance, hazy 5 line appearance or no layering. Hyperechogenic line in the centre represents uterine cavity, outer hyper echogenic lines represent zona basalis and relatively hypoechogenic areas in the middle represent zonal functionalis. Vascularity of the endometrium within zone 3 (hypoechoic layer) was assessed by doppler. Uterine artery pulsatility index was measured from flow velocity waveforms as systolic peak velocity minus diastolic peak velocity divided by mean of the two. No difference in uterine artery PI of left and right side was observed, so average PI was taken into consideration. Myometrium was examined for homogeneity and blood flow internal to arcuate vessels.

Each parameter of Applebaum was scored as follows:

1. Endometrial thickness
   a. <7 mm =0
   b. 7-9 mm = 2
   c. 10-14 mm = 3
   d. > 14 mm = 1
2. Endometrial layering
   a. No layering =0
   b. Hazy five-line appearance =1
   c. Distinct five-line appearance =3
3. Myometrial contractions (seen as wave-like endometrial motion high-speed playback fromvideotape)
   a. <3 contractions in 2 minutes (real-time) =0
   b. >3 contractions in 2 minutes (real-time) =3
4. Myometrial echogenicity
   a. Coarse/inhomogeneous echogenicity =1
   b. Relatively homogeneous echogenicity =2
5. Uterine artery Doppler flow
   a. PI>3.0 =0
   b. PI–2.5-2.99 =0
   c. PI–2.2-2.49 =1
   d. PI < 2.19 = 2

6. Endometrial blood flow within zone 3
   a. Absent = 0
   b. Present, but sparse = 2
   c. Present multifocally = 5
7. Myometrial blood flow internal to the arcuate vessels seen on gray-scale examination
   a. Absent = 0
   b. Present = 2

RESULTS

The age group of patients in both cases and controls were in the range of 20-35 years. Of the 4129 patients who visited our gynaecological out patient department during the study period, 152 patients had history of recurrent pregnancy loss. The incidence of recurrent pregnancy loss at our center was found to be 3.68%.

Endometrial thickness was in the range 10-14 mm in 9.3% of group 1 patients compared with 48.6% of group 2 patients (Fig. 1). In our study 51.1% of patients had hazy 5 line appearance of the endometrium. Uterine artery pulsatility index was measured with value >3 seen in 48.8% of group 1 (Fig. 2). 44.18% and 51.1% of group 1 had no endometrial blood flow within zone 3 and no myometrial blood flow internal to arcuate vessels respectively. 65.1% of cases had inhomogeneous myometrium (Fig. 3). All these values were statistically significant. In our study it was reported that the incidence of recurrent pregnancy loss is higher in women with total Applebaum score of less than 13 as compared to individuals with a total score more than this value. The sensitivity of 90.70% and specificity of 81.08% showed that scoring method can be used for prediction of implantation in patients with recurrent pregnancy loss.

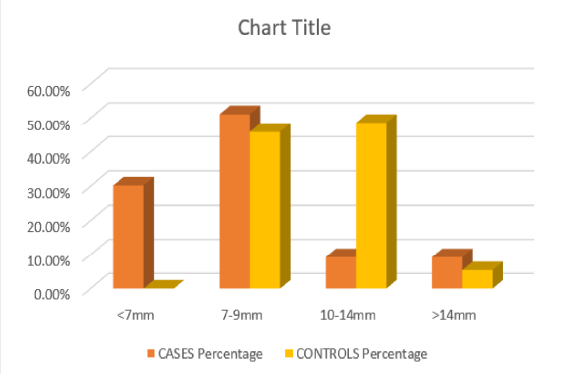


Fig. 1: Bar graph depicting percentage distribution of endometrial thickness among cases and controls

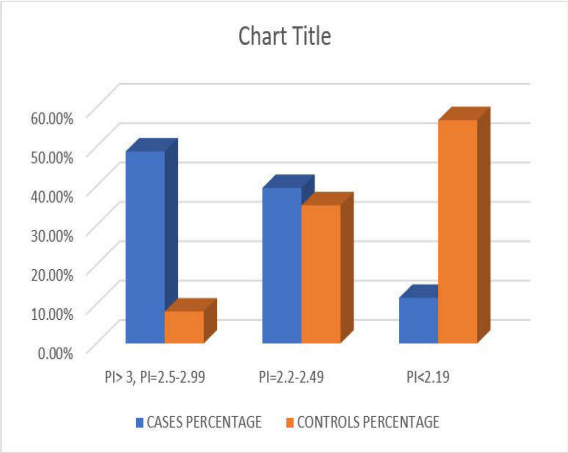


Fig. 2: Bar graph depicting percentage distribution of uterine artery Doppler among cases and controls

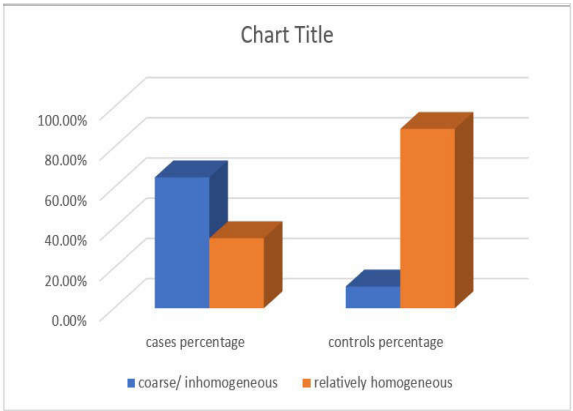


Fig. 3: Bar graph depicting percentage distribution of myometrial echogenecity among cases and controls.

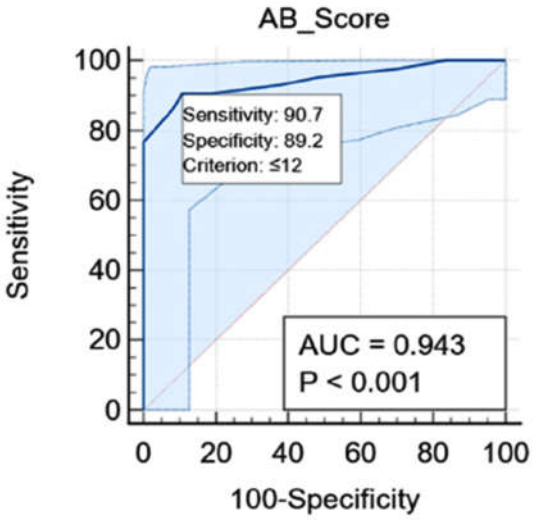


Fig. 4: area under the curve for total Applebaum score among cases and controls

Table 1: Comparison of endometrial parameters among cases and controls

Parameter	Cases		Controls		Odds ratio	95% Confidence interval	P-value
	No.	Percentage	No.	Percentage			
Endometrial thickness (10-14mm)	4	9.3	18	48.6	4.9	2.1-11.2	<0.001
Endometrial layering (no layering)	13	30.2	2	5.4	2.9	1.1-7.5	0.032
Uterine artery Doppler flow (PI<2.19)	5	11.6	21	56.75	3.6	1.5-8.7	0.004
Endometrial blood flow (absent)	19	44.18	1	2.7	9.6	2.23-45.5	0.004

Table 2: Comparison of myometrial parameters among cases and conytrols

Parameter	Cases		Controls		Odds ratio	95% Confidence interval	P value
	No.	Percentage	No.	Percentage			
Myometrial contractions (<3)	27	62.7	4	10.8	11.6	3.8-43.5	<0.001
Myometrial echogenicity (inhomogeneous)	28	65.1	4	10.8	13.2	3.3-52.6	<0.001
Myometrial blood flow (absent)	22	51.1	10	27.02	1.1	0.22-3.5	0.871

Table 3: Criterion values and coordinates for ROC curve for total applebaum scoring

Criterion	Sensitivity	95% CI	Specificity	95% CI	+LR	-LR
<2	0.00	0.0 - 8.2	100.00	90.5 - 100.0	-	1.00
≤10	76.74	61.4 - 88.2	100.00	90.5 - 100.0	-	0.23
≤11	86.05	72.1 - 94.7	91.89	78.1 - 98.3	10.61	0.15
≤12	90.70	77.9 - 97.4	89.19	74.6 - 97.0	8.39	0.10
≤13	90.70	77.9 - 97.4	81.08	64.8 - 92.0	4.79	0.11
≤14	93.02	80.9 - 98.5	62.16	44.8 - 77.5	2.46	0.11
≤15	95.35	84.2 - 99.4	51.35	34.4 - 68.1	1.96	0.091
≤16	97.67	87.7 - 99.9	29.73	15.9 - 47.0	1.39	0.078
≤17	100.00	91.8 - 100.0	16.22	6.2 - 32.0	1.19	0.00
≤20	100.00	91.8 - 100.0	0.00	0.0 - 9.5	1.00	-

DISCUSSION

Unexplained RPL is a very challenging clinical scenario and since the process of implantation is a complex mechanism with enormous changes in the endometrial physiology along with immunomodulation, we undertook this study with an aim to evaluate the uterus by using applebaum scoring in such cases so that specific intervention can be directed to improve the pregnancy outcome.

4129 patients visited our gynaecological OPD during the study period, 152 patients were found to be cases of RPL. The incidence of RPL at our centre was found to be 3.68% which was higher than the incidence in the general population which may be because our centre is a tertiary care centre where patients are being referred.

In our study, it was reported that the incidence of recurrent pregnancy loss was more when endometrial thickness <7mm which was statistically significant (table 1). Similar finding was reported by Mohd Shoeb khan *et al*[7]. In his study, no pregnancy was reported when endometrial thickness was <7mm. When the thickness measured by ultrasound was <7mm, the functional layer was thin or absent, and the implanting embryo would be much closer

to the spiral arteries and higher vascularity and oxygen concentrations of basal endometrium. The high oxygen concentrations near the basal layers could be detrimental compared with usual low oxygen tension of surface endometrium. Noyes *et al*[8], Kovacs *et al*[9] reported that increased endometrial thickness was significantly associated with higher pregnancy rates. In a study conducted by Shu-Yin Tan *et al*[10] it was concluded that predictive accuracy of endometrial thickness to determine miscarriage before 12 weeks of gestation in participants was 68.1%. In a recent study, it was found that pregnancy was positively associated with increasing endometrial thickness.

In our study, it was found that women with recurrent pregnancy loss had hazy 5 line appearance of endometrium as compared to women with no history of recurrent pregnancy loss who had distinct 5 line appearance of the endometrium (table 1). Similar conclusions were drawn from a study conducted by Mohd Shoeb Khan *et al*[7]. Zhao *et al*. concluded that endometrial thickness and pattern independently affect pregnant outcomes.[11]

In our study the average PI of uterine artery was higher in patients with recurrent pregnancy loss as compared to those with no pregnancy losses (table 1). Diastolic blood flow may be categorized as reduced or absent blood flow velocity. Good uterine perfusion, as shown by full diastolic blood flow with low resistance during the early or mid secretory phases, correlates with conception. Ruiqing Tong *et al* it concluded that spiral artery blood flow parameters, and uterine artery blood flow parameters can be effective indices for evaluating endometrial receptivity.[12] In a study conducted by Mohd Shoeb Khan *et al.* it was concluded that average PI of uterine artery was higher in nonconception cycles as compared to conception cycles.[7] In their study, no conception was reported when PI was more than 2.8.

In our study, the incidence of recurrent pregnancy loss was significantly higher in patients with no demonstrable blood flow within zone 3 as compared to those with multifocal vascularity within zone 3 (table 1). Similar finding was reported by Chien *et al*[13], Shu-Yin Tan *et al*[10], and Maugey-Laulon *et al*.

In our study we found that non homogeneous myometrium had a significantly higher chance of RPL as compared to those with relatively homogeneous myometrium (table 2). Zhaojuan *et al* concluded that patients with non homogeneous myometrium on embryo transfer day usually have lower pregnancy rates.[14]

In a recent study, it was shown that combination of endometrial pattern and its thickness, and end diastolic blood flow of uterine artery was most effective for evaluation of endometrial receptivity.

Applebaum reported a pregnancy rate of 100% in females with a score of 20, 80% in females with scores of 17–19, and 60% in women with scores of 14–16. In our study it was reported that for a total score between 10-11, the sensitivity for predicting implantation decreased whereas specificity increased. For a total score between 15-20, the sensitivity for predicting implantation increased whereas specificity decreased. In our study it was found that the incidence of RPL was higher in women with total applebaum score of less than 13 as compared to individuals with a score more than this value. The sensitivity of 90.70% and specificity of 81.08% showed that scoring method can be used for prediction of implantation in patients with recurrent pregnancy loss. For a total score of <12, sensitivity of predicting implantation in case of recurrent pregnancy loss was 90.70% with similar specificity. (table 3)

CONCLUSION

RPL being an enigmatic entity involving a lot of controversies with respect to evaluation and management, Applebaum scoring system can prove to be a non invasive, cost effective intervention in patients with recurrent pregnancy loss to predict the implantation rate. The underlying cause being, the poor endometrial receptivity can be managed effectively by specific interventions that can be directed to increase endometrial thickness, its vascularity and thereby receptivity.

REFERENCES

1. Ruth Bender *et al*, ESHRE guideline: recurrent pregnancy loss, Human Reproduction open volume 2018, issue 2, 2018.
2. Practice Committee of the American Society for Reproductive Medicine. Definitions of infertility and recurrent pregnancy loss. Fertil Steril. 2013;99 (1):63.
3. Ansari AH, Kirkpatrick B. Recurrent pregnancy loss. An update. J Reprod Med. 1998 Sep;43(9):806-14. [PubMed].
4. Hertig AT, Rock J, Adams EC. A description of 34 human ova within the first 17 days of development. Am J Anat 1956 May;98(3):435-493.
5. Croxatto HB, Diaz S, Fuertealba BA, *et al*. Studies on the duration of egg transport in human oviduct. Fertil Steril 1972 Jul;23(7):447-458.

6. Buster JE, Bustilo M, Rodi IA, *et al*. Biologic and morphologic development of donated human ova recovered by nonsurgical uterine lavage. Am J ObstetGynecol 1985 Sep;153(2):211-217.
7. Mohd Shoeb Khan, Aneesa Shaikh, Rekha Ratnani, Ultrasonography and Doppler Study to Predict Uterine Receptivity in Infertile Patients Undergoing embryo Transfer 15 April 2015/ Accepted: 1 July 2015 / Published online: 8 September 2015.
8. Noyes N, Hampton BS, Berkeley A, *et al*. Factors useful in predicting the success of oocyte donation: a 3-year retrospective analysis. Fertil Steril. 2001;76(1):92–97. doi: 10.1016/S0015-0282(01)01823-4. [PubMed] [CrossRef] [Google Scholar].
9. Kovacs P, Matyas S, Boda K, *et al*. The effect of endometrial thickness on IVF/ICSI outcome. Hum Reprod. 2003;18(11):2337–2341.
10. Shu- Yin Tan, Fu Hang, G Purvarshi, *et al*; Decreased endometrial vascularity and receptivity in unexplained recurrent miscarriage patients during mid luteal and early pregnancy phases; Taiwan J ObstetGynaecol: 2015 Oct;54(5):522-6.
11. Jing Zhao, Qiong Zhang, Y Li; The effect of endometrial thickness and pattern measured by ultrasonography on pregnancy outcomes during IVF-ET cycles; Reprod Biol Endocrinol 2012, 10:100.
12. Ruiqing Tong, Ying Zhou, Qi He, *et al*; Analysis of the guidance value of 3D ultrasound in evaluating endometrial receptivity for frozen-thawed embryo transfer in patients with repeated implantation failure; Ann Trnsl Med. 2020 Aug; 8(15): 944.
13. Li-Wei Chien, Heng-Kien Au, Ping-Ling Chen, *et al*. Assessment of uterine receptivity by the endometrial-subendometrial blood flow distribution pattern in women undergoing invitro fertilization-embryo transfer, Fertil Steril 2002 Aug;78(2):245-51. doi: 10.1016/s0015-0282(02)03223-5.
14. Zhaojuan Hou, Qiong Zhang, Jing Zhao, *et al*; Value of endometrial echo pattern transformation after HCG trigger in predicting IVF pregnancy outcome: a prospective cohort study; Reprod Biol Endocrinol 2020 September 8; 18:92.

Original Article

Indian Journal of Obstetrics and Gynecology
Volume 12 Number 2, April – June 2024
DOI: http://dx.doi.org/10.21088/ijog.2321.1636.12224.3

Can Probiotics Play a Major Role as an Adjunctive Therapy in Treatment of Bacterial Vaginosis?

Bandana Sharma[1], Pavika Lal[2], Rashmi Yadav[3], Divya Dwivedi[4], Himani Malviya[5]

How to cite this article:
Bandana Sharma, Pavika Lal, Rashmi Yadav *et al*. Can Probiotics Play a Major Role as an Adjunctive Therapy in Treatment of Bacterial Vaginosis?. Indian J Obstet Gynecol. 2024;12(2):63-69.

Abstract

Background: Bacterial Vaginosis is one of the most common causes of abnormal vaginal discharge in women of reproductive age, which can have a major impact on quality of life. Although the treatment course of oral metronidazole for 7 days results in curative rate of 70%–80% at four weeks of treatment, but is associated with high rates of recurrence occurred within twelve months, reaching up to 40%–50%.

Methods: A Randomized Prospective Interventional Study was done on 1000 reproductive age group females (pregnant or non-pregnant) diagnosed with bacterial vaginosis from November 2020 to October 2022 at department of Obstetrics & Gynaecology, Kanpur. The study group were divided into two subgroups - Group 1 were given metronidazole 500 mg for 7 days and probiotics for 14 days and group 2 were given metronidazole 500 mg for 7 days and placebo for 14 days. The patients were followed after 3 months to know the recurrence.

Results: Majority of patients belonged to rural background (63.1%) with lower socioeconomic (46.6%) and belong to age group 20-35 years. It was observed that there was significant change in Amsel's criteria and Nugent's scoring in Group 1 as compared to Group 2. The rate of recurrence at the end of the treatment for Amsel's criteria in group 1 were 1.03 as compared to group 2 was 1.68 and for Nugent's scoring, the rate of recurrence at the end of treatment in group 1 was 3.17 as compared to group 2 was 4.78.

Conclusion: Probiotics can be considered as one the adjuvant therapy for treating bacterial vaginosis and re-establishing equilibrium in the vaginal microflora thus, preventing the recurrences.

Keywords: Bacterial Vaginosis; Reproductive age group females; Probiotics; Recurrence.

Author's Affiliation: [1]Professor, [2-4]Associate Professor, [5]Senior Resident, Department of Obstetrics and Gynaecology, Ganesh Shankar Vidyarthi Memorial Medical College, Kanpur 208002, India.

Corresponding Author: Himani Malviya, Senior Resident, Department of Obstetrics and Gynaecology, Ganesh Shankar Vidyarthi Memorial Medical College, Kanpur 208002, India.

E-mail: himanimalviya@gmail.com

Received on: 30.07.2024

Accepted on: 16.08.2024

INTRODUCTION

Vaginal discharge is a very common ailment in women of reproductive age which many a time can be attributed to bacterial vaginosis (BV). This condition is often linked to various complications, such as post-hysterectomy vaginal infections and adverse pregnancy outcomes, including premature rupture of membranes, preterm labour, chorioamnionitis, and postpartum endometritis. Additionally, BV increases the risk of contracting human immunodeficiency virus (HIV). Treatment typically involves a 7-day course of oral

metronidazole, with cure rates ranging from 70% to 80% after 4 weeks.[1] However, the recurrence rateis as high as 40%-50% within twelve months.[2]

The vaginal flora is primarily composed of Lactobacillus species, such as L. crispatus, L. jensenii, L. iners, and L. gasseri,[3-5] which help maintain a healthy vaginal environment by producing lactic acid and other antimicrobial substances. However, in bacterial vaginosis (BV), this balance is disrupted. There is a significant shift in the vaginal microbiota, characterized by a decrease in lactobacilli and an overgrowth of various anaerobic bacteria. These include Gardnerella vaginalis, Mycoplasma hominis, Prevotella, Peptostreptococcus, Mobiluncus, and Bacteroides species. This imbalance can lead to various symptoms and complications associated with BV.

The primary recommended first-line treatment for bacterial vaginosis (BV) involves either oral or vaginal administration of metronidazole or clindamycin.[6] These antibiotics, despite having different spectra of activity, have been found to have comparable short-term efficacy. Studies indicate that cure rates range from 80% to 90% within one month after treatment.[7] However, the treatment of BV is complicated by a high relapse rate. Up to 30% of women experience a recurrence of symptoms within one month of completing therapy. This recurrence is particularly notable among those who were treated with topical antibiotics compared to those who received systemic (oral) antibiotics.[8,9] The reasons for the higher relapse rates with topical treatments are not fully understood but may be related to differences in how the drugs distribute and act within the body.

The exact reasons for recurrences of bacterial vaginosis (BV) remain unclear, whether recurrences are due to the failure to fully eradicate the causative organisms during initial treatment or reinfection from sexual partners.[10] Despite the ambiguity, several studies suggest that adjunctive treatment with oral or vaginal probiotics could potentially reduce recurrence rates by restoring the natural balance of the vaginal microbiota. However, this approach has not yet been incorporated into the guidelines of major professional bodies such as the American College of Obstetricians and Gynecologists (ACOG) and the Royal College of Obstetricians and Gynaecologists (RCOG).Given the promising but not yet conclusive evidence, our study aims to investigate the role of probiotics in reducing the recurrence rate of BV. By conducting a detailed analysis, we hope to provide more definitive answers regarding the efficacy of probiotics as an adjunctive treatment, which could potentially inform future guidelines and offer new strategies for managing this common and troublesome condition.

Probiotics, particularly those containing Lactobacillus strains, can help in the following ways:

1. Restoring Lactobacillus Dominance: Probiotics introduce beneficial Lactobacillus bacteria into the vagina, helping to re-establish a healthy microbial balance.
2. Producing Lactic Acid: Lactobacillus bacteria produce lactic acid, which lowers the vaginal pH, creating an acidic environment that is inhospitable to harmful bacteria.
3. Producing Antimicrobial Substances: These beneficial bacteria produce substances like hydrogen peroxide and bacteriocins, which inhibit the growth of pathogenic bacteria.
4. Enhancing Immune Response: Probiotics can enhance the local immune response, helping the body to better fight off infections.
5. Biofilm Disruption: Some probiotics can disrupt biofilms formed by pathogenic bacteria, making them more susceptible to the body's defenses and treatments.

METHODS & MATERIALS

Setting: This was a randomized prospective interventional study conducted in department of obstetrics and gynaecology, GSVM Medical college, Kanpur, Uttar Pradesh, India, over period of two years. All non-pregnant females between age group of 18-45 years, who fulfil ¾ Amsel's criteria and willing to participate were enrolled for the study. Those patients who were under 18 or over 45 years of age, those with diabetes or other chronic illnesses, and those taking oral contraceptive pills were excluded from the study.

After obtaining written and informed consent and ethical clearance from the institutional ethics committee in Kanpur, a total of 1000 females who attended the gynecological OPD with complaints of vaginal discharge were recruited. Vaginal smears were collected for Gram staining, and Nugent's classification was performed only if BV was diagnosed on the basis of Amsel's criteria. The patients were equally divided into two groups: Group 1 received oral metronidazole 400 mg twice daily for 7 days along with oral probiotics capsule Florita twice daily for 14 days, while

Group 2 received oral metronidazole 400 mg twice daily for 7 days along with placebo for 14 days. Post-treatment, patients were followed up after 3 months to assess recurrence of symptoms, and Amsel's criteria and Nugent's score were repeated for objective assessment.

RESULTS

Rural areas were where most of the patients were located, with mostly being 18-25 years old, having low socio-economic status, having primary education. Most of the patients were not pregnant when the study was conducted. (Table 1)

Table 1: Distribution of the Participants in Terms of 'sociodemographic factors'

Socio-demographic factors	Group		
	Group 1	Group 2	Total
Age Group			
18-25 Years	237 (47.4%)	250 (50.0%)	487 (48.7%)
26-35 Years	253 (50.6%)	225 (45.0%)	478 (47.8%)
>35 Years	10 (2.0%)	25 (5.0%)	35 (3.5%)
Socioeconomic - Status			
Upper	106 (21.2%)	106 (21.2%)	212 (21.2%)
Middle	161 (32.2%)	161 (32.2%)	322 (32.2%)
Lower	233 (46.6%)	233 (46.6%)	466 (46.6%)
Residence			
Rural	320 (32.0%)	311 (31.1%)	631 (63.1%)
Urban	180 (18.0%)	189 (18.9%)	369 (36.9%)
Level of Education			
Illiterate	65 (6.5%)	67 (6.7%)	132 (13.2%)
Primary Level	233 (23.3%)	236 (23.6%)	469 (46.9%)
Middle level	144 (14.4%)	135 (13.5%)	279 (27.9%)
Secondary level	58 (5.8%)	62 (6.2%)	120 (12.0%)
Currently Pregnant			
Yes	186 (37.2%)	188 (37.6%)	374 (37.4%)
No	314 (62.8%)	312 (62.4%)	626 (62.6%)

In Group: 1 the mean Amsel's Criteria decreased from a maximum of 3.42 at the start of treatment to a minimum of 1.03 at follow-up period whereas, in Group: 2, the mean Amsel's Criteria decreased from a maximum of 3.43 at the start of treatment to a minimum of 1.68 at follow up period. The overall change in Amsel's Criteria overtime compared in the two groups using the Generalized Estimating Equations method. There was a significant difference in the trend of Amsel's Criteria at the end of follow up between the two groups (p= <0.001). (Table 2)

Table 2: Comparison of the two study Groups with respect to change in Amsel's Criteria over time

Amsel's Criteria	Group		P-value for comparison of the two groups at each of the timepoints (Wilcoxon-Mann-Whitney Test)
	Group I	Group II	
	Mean (SD)	Mean (SD)	
Baseline	3.42 (0.55)	3.43 (0.55)	0.783
Follow-Up	1.03 (1.05)	1.68 (1.54)	<0.001
P Value for change in Amsel's Criteria over time within each group (Wilcoxon Test)	<0.001	<0.001	–
Overall P Value for comparison of change in Amsel's Criteria over time between the two groups (Generalized Estimating Equations)	<0.001		

The following line diagram depicting the change in Amsel's Criteria from the start of treatment to at the end of follow up period in between the two groups. This line diagram shows that there is more decrease in Amsel's criteria in group1as compare to group 2. (Fig. 1)

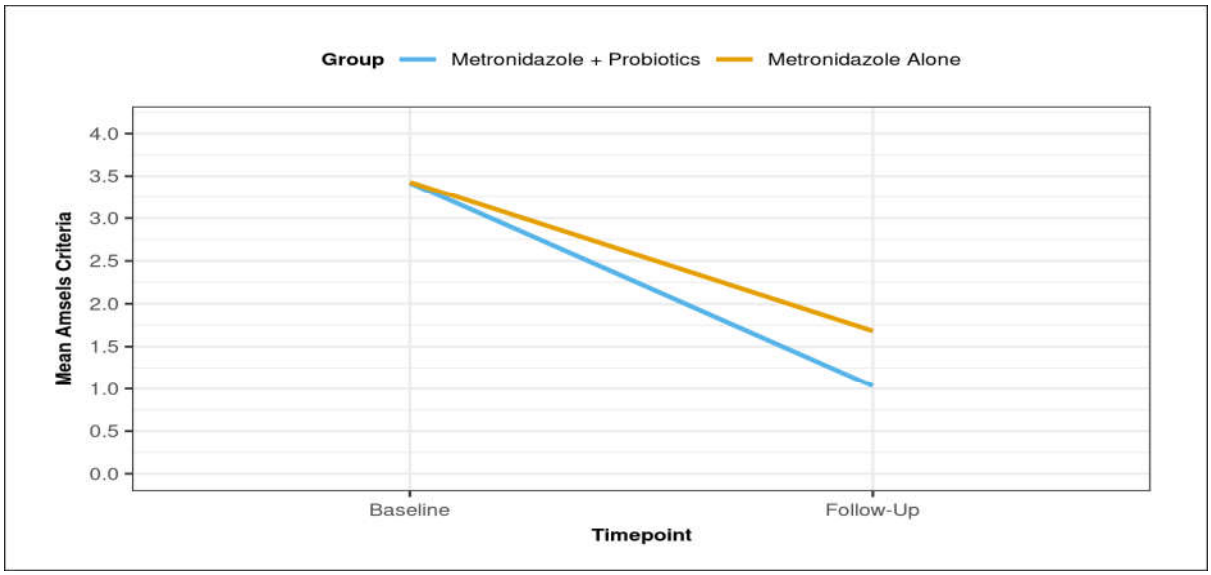


Fig. 1: Change in Amsel's Criteria Over Time

In Group 1, the mean Nugent's Scoring decreased from a maximum of 8.45 at the treatment to a minimum of 3.17 at the Follow-Up period whereas, in Group: 2, the mean Nugent's Scoring decreased from a maximum of 8.46 at the start of the treatment to a minimum of 4.78 at the Follow-Up period. The overall change in Nugent's Scoring overtime was compared in the two groups using the Generalized Estimating Equations method. There was a significant difference in the trend of Nugent's Scoring at the end of follow up between the two groups (p=<0.001). (Table 3)

Table 3: Comparison of the two study Groups with respect to change in Nugent's Scoring over time

Nugent's Scoring	Group		P-value for comparison of the two groups at each of the time points (Wilcoxon-Mann-Whitney Test)
	Metronidazole + Probiotics	Metronidazole Alone	
	Mean (SD)	Mean (SD)	
Baseline	8.45 (0.52)	8.46 (0.53)	0.781
Follow-Up	3.17 (2.42)	4.78 (3.10)	<0.001
P Value for change in Nugent's Scoring over time within each group (Wilcoxon Test)	<0.001	<0.001	
Overall P Value for comparison of change in Nugent's Scoring over time between the two groups (Generalized Estimating Equations)	<0.001		

The following line diagram depicting the change in Nugent's Scoring from the start of treatment to at the end of follow upper iodin between the two groups. This line diagram shows that there is more decrease in Nugent's Scoring in group 1 as compare to group 2. (Fig. 2)

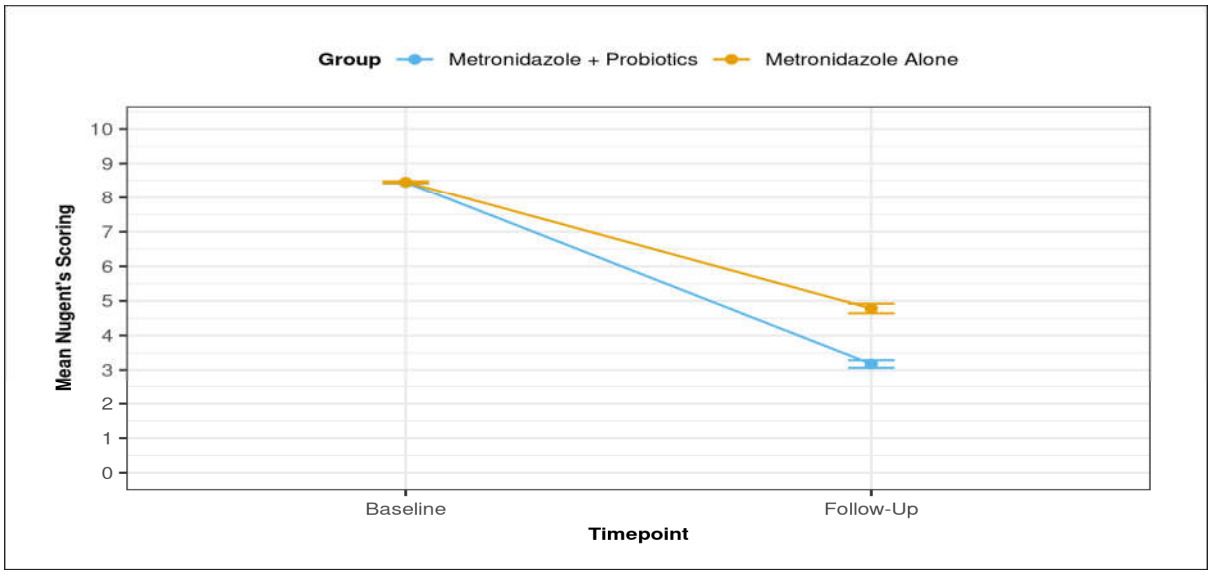


Fig. 2: Change in Nugent's Scoring Over Time

DISCUSSION

In our study, the majority of patients fell within the age group of 20-35 years, with a mean age of 26.4 years. This finding aligns with the research by Mtebe V. Majigo *et al*[11], which reported a median age of 29 years for BV. Although Bacterial vaginosis is not considerd as a STD but it is more prevalent in this age group due to their increased frequency of sexual activity.

In our study, majority of patients belonged to rural areas (63.1%) and had primary level education (46.9%), with poor personal hygiene practices. Yiewou Marguerithe Kamga *et al*[12] demonstrated that bacterial vaginosis was significantly more prevalent in women from rural areas compared to urban areas (29.5% vs. 24.5%, $\chi 2 = 8.609$, $p = 0.014$). Additionally, they found that bacterial vaginosis was more common among individuals with a primary level of education (33.3%) compared to those with higher education level. This finding was also observed in our study, possibly indicating increased awareness and adherence to personal hygiene practices among individuals with higher education level.

In our study, a significant proportion of patients were from low socio-economic status (46.6%), underscoring the disproportionate burden of bacterial vaginosis on the underprivileged segment of society. T. Ashraf-Ganjoe *et al*.[13] also found that patients with BV had significantly lower educational ($p = 0.006$) and socioeconomic ($p = 0.021$) levels. In our study, the majority of patients presented with white discharge (93.2%), followed by backache (57.4%), which aligns with the findings reported by Eriksson K *et al*.

In Group 1 (Metronidazole + Probiotics), the mean Amsel's Criteria decreased significantly from a maximum of 3.42 at the start of treatment to a minimum of 1.03 after 3 months (Wilcoxon Test: $V = 105934.0$, $p < 0.001$). Similarly, in Group 2 (Metronidazole Alone), the mean Amsel's Criteria decreased from a maximum of 3.43 at the beginning of treatment to a minimum of 1.68 at the end of treatment, showing a statistically significant change within the group (Wilcoxon Test: $V = 73571.0$, $p < 0.001$). Comparing the trend of Amsel's Criteria over time between the two groups using Generalized Estimating Equations revealed a significant difference ($p < 0.001$). These findings were consistent with a study conducted by Nadia Recine *et al*.[14] in 2015 (15), where participants were divided into Group A (standard treatment for BV—metronidazole 500 mg orally twice a day for 7 days) and Group B (same antibiotic regimen followed by vaginal tablets containing Lactobacillus rhamnosus BMX 54). The study found that vaginal flora was significantly restored in Group B patients after 2 months compared to Group A ($p = 0.014$).

In Group 1 (Metronidazole + Probiotics), the mean Nugent's Scoring decreased significantly from a maximum of 8.45 at the initiation of treatment to a minimum of 3.17 after 3 months ($p < 0.001$). Similarly, in Group 2 (Metronidazole Alone), the mean Nugent's Scoring decreased from a maximum of 8.46 at the start of treatment to a minimum

of 4.78 after 3 months, showing a statistically significant change ($p < 0.001$). Comparing the trend of Nugent's Scoring over time between the two groups revealed a significant difference ($p < 0.001$). These findings align with a study conducted by R.S. Vigneshwari *et al*. in 2014[15], where they observed significant symptomatic improvement and Nugent scoring improvement in the Metronidazole + probiotics group compared to the Metronidazole alone group ($p < 0.05$).

In our study, the recurrence of bacterial vaginosis (BV) was observed more frequently in the metronidazole alone group compared to the group receiving metronidazole along with probiotics. These findings were consistent with other studies, such as the one conducted by Wei Keong Chieng *et al*.[16], where probiotics were shown to reduce the risk of BV recurrences by 45% compared to either placebo or metronidazole (14.8% vs. 25.5%, RR: 0.55, $p = 0.03$). Similarly, H-F. Liu, N. Y *et al*.[17] found that in the subgroup analysis of antibiotic plus probiotics versus antibiotics alone, the antibiotic plus probiotics group had a significantly lower BV recurrence rate at 1-3 months (RR: 0.302, 95% CI: 0.172-0.532) and overall BV recurrence rate (RR: 0.419, 95% CI: 0.238-0.737) than the antibiotics alone group.

Strength of the study

The present study assessed a larger sample which added to the scarce literature available on use of probiotics in treatment of Bacterial Vaginosis especially in Indian population.

Limitation of the study

» The sample does not reflect the actual demographic composition of the target population which also restricts the generalizability of the findings.

CONCLUSION

- From our study, we can conclude that while conventional treatment with oral metronidazole for 7 days was effective in the majority of patients, recurrence was common even after completing the recommended course. This highlights the concern of repeated antibiotic use leading to potential resistance.
- In our study, we found that adding probiotics to the standard treatment regimen showed promising results with regard to reduction in recurrence rates of bacterial vaginosis. Furthermore, the safety profile of probiotics appeared to be favorable, as no major side effects were observed.

Indeed, incorporating probiotics into the standard antibiotic therapy for bacterial vaginosis (BV) could prove to be a valuable adjunct in reducing the frequency of recurrences. This combined approach may offer benefits in restoring and maintaining a healthy vaginal microbiota, thereby potentially improving treatment outcomes. Considering the promising results observed in various studies, the inclusion of probiotics alongside antibiotics warrants consideration as a complementary strategy for managing BV. However, further research and clinical trials are needed to validate its efficacy and establish optimal treatment protocols.

REFERENCES

1. Ziyadi S., Homayouni A., Mohammad-Alizadeh-Charandabi S. *et al*, Probiotics Prebiotics & Symbiotic. Elsevier Inc.; Amsterdam, The Netherlands: 2016. Chapter 49—Probiotics and Usage in Bacterial Vaginosis; pp.55–659.
2. Balkus J.E., Srinivasan S., Anzala O., Kimani J., *et al*, Impact of periodic presumptive treatment for bacterial vaginos is on the vaginal microbiome among women participating in the Preventing Vaginal Infections trial, Infectious Disease. 2017 march 1; 215: jiw 622. doi: 10.1093/infdis/jiw622.
3. XZhou, SJ Bent, MG Schneider, CC Davis, *et al*, Characterization of vaginal microbial communities in adult healthy women using cultivation-independent methods, microbiology, 2004 Aug;150(Pt 8):2565-2573,doi:10.1099/mic.0.26905-0.
4. A Vasquez, T Jakobsson, S Ahrne, U Forsum *et al*, Vaginal Lactobacills flora of healthy Swedish women, clinical microbiology, 2002 Aug;40(8):2746-9.doi:10.1128/JCM.40.8.2746-2749.2002.
5. J Butron, P Cardieux, G Reid, Improved understanding of the bacterial vaginal microbiota of women before and after probiotic instillation, Appl environmicrobiology, 2003 Jan; 69(1):97-101. doi:10.1128/AEM.69.1.97-101.2003.
6. Koumans EH, Sternberg M, Bruce C, McQuillan G, Kendrick, Sutton M, Markowitz LE. The prevalence of Bacterial Vaginosis.
7. Austin MN, Beigi RH, Meyn LA, Hillier SL. Microbiologic response to treatment ofbacterial vaginosis with topical clindamycin or metronidazole, J Clin Microbiol, 2005, vol. 43(pg. 4492-7) thesis of data, Clin Infect Dis, 2002, vol. 35Suppl 2(pg. 72)
8. Sobel JD, Schmitt C, Meriwether C. Long-term follow-up of patients with bacterial vaginosis treated with oral metronidazole and topical clindamycin, J Infect Dis, 1993, vol. 167 (pg. 783-4).

9. Centers for Disease Control and Prevention Sexually transmitted diseases treatment Guidel 2002 MMWR Recomm Rep, 2002, vol. 51(pg. 1-78).
10. Koumans EH, Markowitz LE, Hogan V, for the CDC BV Working Group. Indications for therapy and treatment recommendations for bacterial vaginosis in nonpregnant and pregnant women: a syn8
11. Mtebe V Majigo, Paschal Kashindye, Zachariah Mtulo, Agricola Joachim, Bacterial vaginosis, the leading cause of genital discharge among women presenting with vaginal infection in Dar es Salaam, Tanzania, African Health Sciences, 2021 Jun; 21(2):531-537.doi:10.4314/ahs.v21i2.7.
12. Yiewou Margueri the Kamga, John Palle Ngunde, and Jane-Francis K.T. Akoachere, Prevalence of bacterial vaginosis and associated risk factors in pregnant women receiving antenatal care at the Kumba Health District (KHD), Cameroon, BMC Pregnancy Childbirth. 2019;19:166.May10. doi:10.1186/s12884-019-2312-9.
13. T. Ashraf-Ganjoe, Risk factors for bacterial vaginosis in women attending a hospital in Kerman, Islamic Republic of Iran, Eastern Mediterranean HealthJournal,Vol.11,No.3,2005.
14. Nadia Recine, Ettore Palma, Lavinia Domenici, Margherita Giorgini *et al*, restoring vaginal microbiota: biological control of bacterial vaginosis. A prospective case-control study using Lactobacillus romanosus BMX 54 as anadjuvant treatment against bacterial vaginosis, Archives of Gynecology and Obstetrics volume 293, pages101–107, 5 july 2015
15. R.S.Vigneshwari,Rambabu,T.Jeyaseelansenthinath, P. Revathi *et al*, role of probiotics in treatment of bacterial vaginosis, International Journal of scientific and technology, research volume 3, issue 4, April 2014
16. Chieng WK, Abdul Jalal MI, Bedi JS, Zainuddin A A, *et al*, Probiotics, apromising therapy to reduce the recurrence of bacterial vaginosis in women? asystematic review and meta-analysis of randomized controlled trials, Front. Nutr. 9:938838. doi:10.3389/fnut.2022.938838,2022September20
17. H.-F. LIU, N. YI, A systematic review and meta-analysis on the efficacy of probiotics for bacterial vaginosis, European Review for Medical and Pharmacological Sciences 2022;26:90-98.

SUBSCRIPTION FORM

I want to renew/subscribe international class journal "**Indian Journal of Obstetrics and Gynecology**" of Red Flower Publication Pvt. Ltd.

Subscription Rates:
- Institutional: INR 10500/USD 820.31

Name and complete address (in capitals):_____

_____

Payment detail:
Online payment link: http://rfppl.co.in/payment.php?mid=15

Cheque/DD: Please send the US dollar check from outside India and INR check from India made payable to 'Red Flower Publication Private Limited'. Drawn on Delhi branch.

Wire transfer/NEFT/RTGS:
Complete Bank Account No. 604320110000467
Beneficiary Name: Red Flower Publication Pvt. Ltd.
Bank & Branch Name: Bank of India; Mayur Vihar
MICR Code: 110013045
Branch Code: 6043
IFSC Code: BKID0006043 (used for RTGS and NEFT transactions)
Swift Code: BKIDINBBDOS

Term and condition for supply of journals
1. Advance payment required by Demand Draft payable to **Red Flower Publication Pvt. Ltd**. payable at **Delhi.**
2. Cancellation not allowed except for duplicate payment.
3. Agents allowed 12.5% discount.
4. Claim must be made within six months from issue date.

Mail all orders to
Subscription and Marketing Manager
Red Flower Publication Pvt. Ltd.
48/41-42, DSIDC, Pocket-II
Mayur Vihar Phase-I
Delhi - 110 091(India)
Phone: 91-11-79695648
Cell: +91-9821671871
E-mail: sales@rfppl.co.in

Original Article

Indian Journal of Obstetrics and Gynecology
Volume 12 Number 2, April – June 2024
DOI: http://dx.doi.org/10.21088/ijog.2321.1636.12224.4

Clinical Features and Obstetric and Neonatal Outcomes of Pregnant Women with Covid-19: A Prospective, Single Centre Study

Vedavathy Nayak[1], Sreelatha S[2], Shakuntala P N[3], Renuka Ramaiah[4], Sujatha Prabhu[5]

How to cite this article:
Vedavathy Nayak, Sreelatha S, Shakuntala P N *et al.* Clinical Features and Obstetric and Neonatal Outcomes of Pregnant Women with Covid-19: A Prospective, Single Centre Study. Indian J Obstet Gynecol. 2024;12(2):71-75.

Abstract

Aim: This study aims to describe the clinical features, obstetric and neonatal outcome of pregnancies complicated with COVID-19 infection.

Methods: This is a longitudinal, single center, observational study conducted on all COVID-19 positive pregnant women who were admitted in our institution from July 2020 to June 2021. During the study period, a total of 195 pregnant women with COVID-19 infection confirmed by RT PCR test, were admitted and included in the study. Data were collected about the demographic profile, clinical characteristics, maternal and neonatal outcomes.

Results: The mean age was 26 years (SD = 3.48). Majority patients (75.4%) were asymptomatic and 21.5% had mild symptoms. Only 2(1.02%) women had severe COVID pneumonia. Majority (89.6%) were admitted in 3rd trimester. Cesarean section rate in COVID-19 infected pregnant women was 60%. Most neonates were asymptomatic and only 2 of them tested positive on testing within 48 h of birth.

Conclusion: There is no major effect of COVID-19 infection during pregnancy on maternal and neonatal outcome.

Keywords: COVID-19; Obstetric outcome; Neonatal outcome; Pregnancy.

INTRODUCTION

In December 2019, a number of pneumonia cases with no known origin surfaced in Wuhan, China; the cases' clinical manifestations were similar to those of viral pneumonia. A novel coronavirus that was eventually identified as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or COVID-19 was discovered through analysis of nasopharyngeal and oropharyngeal tissues. Since then, the illness spread quickly throughout the world, including India, and the WHO declared it to be a pandemic. There were 1.6 million deaths and 76 million cases worldwide as of December 2020. 9.6 million cases and around 145,000 deaths have been reported in India, and the figure rose daily. Most studies on the outbreak caused by the 2019 novel coronavirus disease (COVID-19) are based on the general population. At the time, information regarding the epidemiology, clinical features, obstetric and neonatal outcomes in pregnant women infected with COVID-19 is scarce

Author's Affiliation: [1]Specialist, Department of Obstetrics and Gynaecology, ESIC model Hospital Peenya, Bengaluru 560022, Karnataka, [2,4,5]Professor, [3]Associate Professor, Department of Obstetrics and Gynaecology, Professor ESIC Model Hospital, Rajajinagar 560010, Bangalore, India.

Corresponding Author: Vedavathy Nayak, Specialist, Department of Obstetrics and Gynaecology, ESIC model Hospital Peenya, Bengaluru 560022, Karnataka, India.

E-mail: vedanarayan97@gmail.com

Received on: 16.08.2024 **Accepted on:** 31.08.2024

and limited data is available for pregnant women with COVID-19 infection. Hence the need for the study. The study aims to evaluate the clinical characteristics, obstetric and perinatal outcome of pregnant women with COVID-19 infection.

AIMS AND OBJECTIVES

i) To study the epidemiological and clinical characteristics of pregnant patients with COVID-19 infection.

ii) To evaluate maternal and perinatal outcome of COVID-19 infection in pregnant women.

MATERIALS AND METHODS

This is a longitudinal observational study done in the Department of OBG, ESIC Medical college PGIMSR and Model Hospital, a tertiary health care hospital and medical college in Rajajinagar, Bengaluru. Pregnant patients who presented to the Department of OBG between July 2020 and June 2021 and tested positive for COVID-19 (SARS CoV-2 infection confirmed using RT-PCR or Rapid Antigen test) comprised the study population. All eligible pregnant COVID-19 positive patients admitted to the hospital during the study period were included in the study through universal sampling. As the period of study coincided with the peak of the covid pandemic, all pregnant women were tested for COVID-19 irrespective of their symptoms as per hospital protocol.

All pregnant women who were diagnosed with COVID-19 infection by the real time RT-PCR test and who were admitted in the hospital's isolation ward were included in the study. On admission, a routine antenatal history was taken and clinical examination done. Apart from this, a thorough history of COVID-19 exposure was taken and signs and symptoms of COVID-19 were looked into. Routine ANC investigations were done. Other specific investigations done were C-reactive protein, D-dimer, LDH and S. Ferritin. (Inflammatory Markers). Written informed consent was taken from all patients. A predesigned proforma was used to obtain demographic and clinical information like Age, Parity, SE status, Gestational age, obstetric history, presence of co-morbdities like anaemia, hypertension, diabetes and hypothyroidism. Exposure to COVID-19 persons, living or travel to containment areas, presence of covid symptoms like fever, cough, sore throat, shortness of breath, diarrhoea were recorded. Mode of delivery, intra or postpartum complications were noted. Neonate's birth weight, Apgar score at birth was seen. All neonates were tested for COVID-19 by real time PCR. Any neonatal complications were recorded.

Statistical analysis: The data was collected in MS Excel and analysed using SPSS version 20.0. The continuous variables were summarized as mean with standard deviation or median with interquartile range based on the distribution of the data. The categorical variables were summarized as frequencies with proportions. ***Ethical considerations:*** The study was conducted after getting approval by the institutional ethics committee. Written informed consent was taken from all patients.

RESULTS

During the period of study, 195 pregnant women diagnosed COVID positive delivered in the obstetrical unit of our department.

The age of confirmed COVID-19 cases ranged from 18 to 35 years with the most common age group being 26-29 years (44.6%). The gestational age on admission ranged from 31 weeks to 40 weeks 5 days with the mean gestational age being 38 weeks 3 days. 80 (41%) women were primigravida and 115 (59%) were multipara. 47 (24.1%) women had a previous LSCS. Associated comorbidities in these women included GDM in 24 women (12.3%), PIH in 6 (3.07%), hypothyroidism in 36 (18.4%) and anaemia (Hb- <10gm/dl) in 9(4.6%).

Table 1: Baseline Characteristics

Age Mean (SD)	**26.57 (3.4845)**
18-20 years	8 (4.1%)
21-25 years	70 (35.9%)
26-29 years	87 (44.6%)
30-39 years	30 (1.5%)
Parity	
Primigravida	80 (41%)
Multigravida	115 (59%)
Gestational Age Mean (SD)	38.39 weeks (1.5368)
<34 weeks	5 (1.9%)
34-36.6 weeks	17 (8.4%)
>37 weeks	173 (89.6%)
Comorbidities	
GDM	24 (12.3%)
PIH/Hypertension	6 (3.07%)
Hypothyroidism	36 (18.4%)
Anaemia	9 (4.6%)
Oligoamnios/IUGR	18 (9.2%)
Previous h/o LSCS	47(24.1%)

Clinical Presentation

Majority of patients ie; 147 of 195 (75.4%) were asymptomatic who were diagnosed on routine testing as per hospital protocol. 19 presented with cold and cough, 8 with fever, 5 with diarrhea, 10 patients had vague symptoms like headache, fatigue, loss of appetite. Over the course of isolation and treatment in hospital, 6 developed fall in Oxygen saturation with 1 patient requiring ICU admission but did not require ventilator support and all 6 recovered completely.[2] women developed severe pneumonia (case of IDDM with diabetic ketoacidosis) (GDM, anaemia, acute respiratory failure) needed ventilator support and succumbed to death.

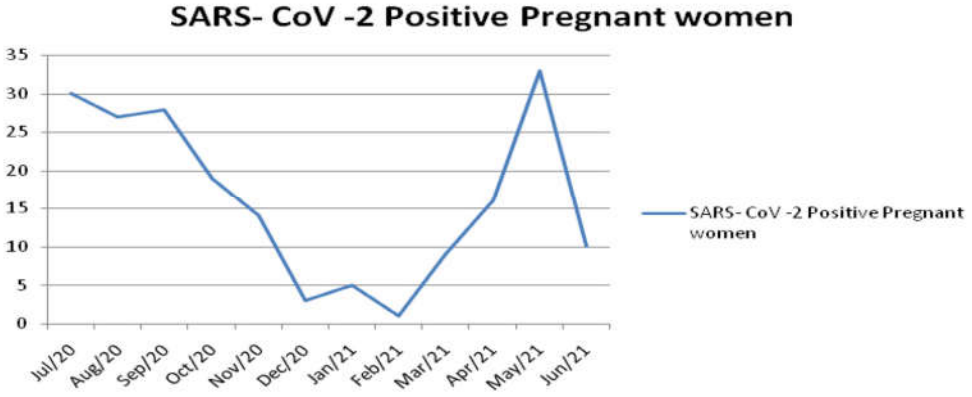


Fig. 1: Month wise number of Covid positive pregnant women

Table 2: Symptoms of COVID-19 (n=154)

Symptoms	Number
Asymptomatic	147 (75.4%)
Mild symptoms	42 (21.5%)
Moderate symptoms	4 (2.05%)
Severe symptoms	2 (1.02%)

Outcome in Covid +ve pregnant women:

Most Covid +ve pregnant women were either asymptomatic or in symptomatically mild category. They were started prophylactically on oseltamivir, ivermectin and multivitamins including zinc and vitamin C. Antibiotic (Azithromycin) were given to counter super added bacterial infections. 6 patients needed oxygen support out of which 2 women were started on LMWH to prevent thromboembolism. 2 of the patients deteriorated to ventilator support. There were 2 maternal deaths during the period of study with a case fatality rate of 1.02%

Obstetrical & Neonatal Outcome: (Table 2)

The mean gestational age at delivery for Covid + ve patients was 38.3 +/- 1.5 weeks. 74 (37.9%) women delivered vaginally, 4(2.05%) had vacuum assisted vaginal delivery and 117 (60%) delivered by caesarean section.

Out of the 195 COVID-19 confirmed deliveries, only 2 (1.2%) of the neonates were found Covid positive on initial testing done 1st day of birth. Both babies tested COVID negative on repeat test after 7 days of the first test and were discharged from NICU.

Table 3: Obstetrical and Neonatal Outcome

Gestational age at delivery mean (SD)	38.39 weeks (1.5368)
<34 weeks	5 (1.9%)
34-36.6 weeks	17 (8.4%)
>37 weeks	173 (89.6%)
Mode of Delivery	
Vaginal	74 (37.9%)
Vacuum assisted	4 (2.05%)
LSCS	117 (60.0%)
Mean Birth Weight (gms) Mean (SD)	2796.116 (416.82)
>2.5 kg	138 (70.78%)
<2.5 kg	57 (29.22%)
Covid Status of Neonates	
Negative	193
Positive	2

DISCUSSION

Human corona virus is one of the most common pathogen that causes respiratory infection.

SARS-COV-2 is an enveloped vision that measure about 50-200 nm in diameter with a single positive sense RNA genome.

In the present study, 75.4% of pregnant Covid + ve patients were asymptomatic and the rest had mild symptoms only. These observations were similar to studies done on COVID-19 confirmed pregnant patients.[1,2] However, other studies have reported up to 88% and 67.4% as symptomatic at the time of presentation.[3,4]

Majority (89.6%) of COVID-19 positive pregnant women in our study presented in the late third trimester. This is similar to a study by Kumari et al.[5] where 75.6% patients presented in the third trimester. Another study reported median age on diagnosis to be 29 weeks and half of them were in third trimester.[3]

In our study, Gestational diabetes mellitus was found to be associated in 9.7% of COVID positive pregnant patients. Other study has also reported increased risk of GDM in pregnancy with SARSCoV2 infection.[6] Evidence of association of hypertensive disorders in pregnant women infected with COVID-19 is reported in some studies. [1] But in our study only 2.6 % of SARSCoV2 infected pregnant patients had hypertension.

Our hospital being a tertiary care referral hospital, number of cesarean sections in COVID positive pregnant women was relatively high (60.39%). Nayak et al.[1] reported a cesarean rate of 50% in COVID-19 infected patients. Ayed et al. [3] reported a cesarean rate of 47.8%. Another study suggested that majority of pregnant women had planned caesarean section to prevent neonatal transmission of the virus.[7]

In our study, only 2 (1.9%) patients had developed severe COVID pneumonia requiring ICU admission and succumbed with a case fatality rate of 1.02%. Various preliminary studies done on COVID positive pregnancies have also suggested low rate of ICU admission and mortality in proportion to the rates among general population.[8,9]

The neonatal outcome in our study was mostly reassuring in consistent with other studies.[5,10] The incidence of preterm births in our study was 8.4%% which is lower in comparison to 27% reported in UKOSS study.[6] Out of 154 deliveries, only 2 neonates tested positive for SARS CoV2 by RTPCR in their initial assessment.

Our study clearly demonstrated that COVID-19 infection in pregnancy did not affect mother and neonate significantly. The strength of our study is its relative large sample size. We acknowledge that the limitation of the study is the lack of a comparison group.

CONCLUSION

There is no major effect of COVID-19 infection in pregnancy on maternal and neonatal outcome.

The majority of expectant mothers infected with COVID-19 either had no symptoms at all or very mild ones, and they were discharged from the hospital without any issues. However, when COVID during pregnancy is complicated by medical conditions like diabetes, serious sickness may result. Larger studies are required to give a clear picture about vertical transmission and other maternal effects of COVID-19 infection. It is critical to monitor the disease's spread and be able to apply outbreak control and management measures as soon as the virus enters a community.

REFERENCES

1. Nayak AH, Kapote DS, Fonseca M, Chavan N, Mayekar R, Sarmalkar M, et al. Impact of the coronavirus infection in pregnancy: A preliminary study of 141 patients. J Obstet Gynecol India 2020;70:25661. 24.
2. Muhidin S, Behboodi Moghadam Z, Vizheh M. Analysis of maternal coronavirus infections and neonates born to mothers with 2019nCoV; A systematic review. Arch Acad Emerg Med 2020;8:e49.
3. Ayed A, Embaireeg A, Benawadh A, AlFouzan W, Hammoud M, AlHathal M, et al. Maternal and perinatal characteristics and outcomes of pregnancies complicated with COVID-19 in Kuwait. BMC Pregnancy Childbirth 2020;20:19. 27.
4. Smith V, Seo D, Warty R, Payne O, Salih M, Chin KL, et al. Maternal and neonatal outcomes associated with COVID-19 infection: A systematic review. PLoS One 2020;15:e0234187.
5. Kumari A, Anand S, Vidyarthi A. Effects of COVID-19 during pregnancy on maternal and neonatal outcome: A retrospective observational study in tertiary teaching hospital, India. J Family Med Prim Care 2022;11:1820-5.
6. Knight M, Bunch K, Vousden N, Morris E, Simpson N, Gale C, et al. Characteristics and outcomes of pregnant women admitted to hospital with confirmed SARS-CoV-2 infection in UK: national population based cohort study. UK Obstetric Surveillance System BMJ. 2020;369:m2107.
7. Yan J, Guo J, Fan C, Juan J, Yu X, Li J, et al. Coronavirus disease 2019 (COVID-19) in pregnant women: A report based on 116 cases. Am J Obstetr Gynecol 2020;223:111.e114.

8. Zaigham M, Andersson O. Maternal and perinatal outcomes with COVID-19: A systematic review of 108 pregnancies. Acta Obstet Gynecol Scand 2020;99:8239.
9. Zeng H, Xu C, Fan J, Tang Y, Deng Q, Zhang W, et al. Antibodies in infants born to mothers with COVID-19 pneumonia. JAMA 2020;323:18489.
10. Antoun L, Toweel NE, Ahmed I, Patni S, Honest H. Maternal COVID-19 infection, clinical characteristics, pregnancy, and neonatal outcome: A prospective cohort study. Eur J Obstet Gynecol Reprod Biol 2020;252:55962.

Original Article

Indian Journal of Obstetrics and Gynecology
Volume 12 Number 2, April – June 2024
DOI: http://dx.doi.org/10.21088/ijog.2321.1636.12224.5

Association of Congenital Thrombophilia in Unexplained Infertility: By Chance or By Cause

Nutan Agarwal[1], Meenakshi Karan[2], Vidushi Kulshrestha[3], Nilanchali Singh[4], Renu saxena[5], Alka Kriplani[6], Neerja Bhatla[7]

How to cite this article:

Nutan Agarwal, Meenakshi Karan, Vidushi Kulshrestha *et al.* Association of Congenital Thrombophilia in Unexplained Infertility: By Chance or By Cause. Indian J Obstet Gynecol. 2024;12(2):77-84.

Abstract

Objective: To find incidence of congenital thrombophilia in unexplained infertility versus fertile female population with intend to determine if thrombophilia is a possible cause and which type of thrombophilia is more prevalent in unexplained infertility.

Methods: Study group (Group A) comprised of 40 infertile patients of age between 20-40 years in whom no cause of infertility was identified. The control group comprised of 40 healthy women with proven fertility, matched for age, with no history of thrombo-embolic events. Both the groups were tested for inherited thrombophilia included Protein C, Protein S, Anti-thrombin III, Activated Protein C Resistance, Homocysteine, factor V Leiden (PCR), Prothrombin G20210 G gene and M THFR (677c/T)gene mutation.

Results: Overall 14 (35%) subjects in the unexplained infertility group, and 5 (12.5%) in the control group were detected with positive thrombophilic factor (p value-0.023). Out of 14 positive cases, 7/14(50%) had more than one factor (35% had 2 and 15% had 3 factors)thus 23 thrombophilia factors in 14 women in group 1 in comparision of onlt 7 in 5 in (2 with 2 factors)group2 (p=0.005). Out of 23, Protein S (10%) and Antithrombin III (10%) had the highest frequency followed by Homocysteine (7.5%), Protein C (7.5%), MTHFR gene mutation (7.5%), prothrombin 20210 (5%), Factor V Leiden (5%) and APCR (5%)in group1 Out of the 7 thrombophilia factors in controls, Factor V Leiden mutation and APCR had the highest frequency (5%) followed by Protein S, Protein C, and Homocysteine (2.5%). APCR and Factor V leiden were similar in both groups whereas Hyperhomocysteinaemia combined with MTHFR gene mutation was more in unexplained infertility andprothrombin gene was found only in unexplained infertility

Conclusion: There is significant association of thrombophilia with unexplained infertility Hyperhomocystinaemia combined with MTHFR gene mutation and APCR with prothrombin gene mutation are more likely to be associated with unexplained infertility. Thrombophilia evaluation may be included along with other tests in evaluation of unexplained infertility.

Keywords: Unexplained Infertility, Congenital Thrombophilia.

Author's Affiliation: [1]Former Professor, [2]Ex Resident, [3]Additional Professor, [4]Associate Professor, [5-7]Ex-Head of the Department, Department of Obstetrics and Gynecology, [2,4,5]Professor, [3]Associate Professor, Department of Obstetrics and Gynecology, Professor All India Intitute of Medical sciences, New Delhi 110029, Delhi, India.

Corresponding Author: Nutan Agarwal, Former Professor, Department of Obstetrics and Gynaecology, All India Intitute of Medical sciences, New Delhi 110029, Delhi, India.

E-mail: nutan_agarwal@yahoo.com

Received on: 01.08.2024

Accepted on: 31.08.2024

INTRODUCTION

Infertility affects between 15 to 20% couples of reproductive age and is a major health issue. Despite the best available assisted reproduction techniques there is a large no of patients who are not able to conceive. Nearly 1/3rd of patients of infertility are unexplained infertility, in which no abnormality is revealed and treatment is only empirical which may include expectant observation, ovulation induction, intrauterine insemination or even in vitro fertilization.[1]

Undiagnosed early pregnancy loss or biochemical pregnancy loss may also be a cause of infertility. The majority of studies conducted to evaluate failure to conceive in assisted reproduction have focused on the problems that occur following laboratory fertilization i.e. implantation of the embryo in the woman's uterus.[2] Factors that need to be taken into consideration include improving endometrial receptivity and identifying intervening factors associated with immunological response and the genetic characteristics of the woman, including her potential for thrombosis during pregnancy and implantation of the embryo.[3] Recently, a hypothesis has been raised that the same factors of thrombosis associated with the occurrence of recurrent pregnancy loss may also affect the early phase of the embryo implantation process and leading to infertility[2], however, there is no consensus in the literature on this subject. The haematological changes that lead to hypercoagulability, with a consequent increase in the occurrence of thrombosis, have been cited as factors that hamper the process of embryo implantation.[2,4,5] Hence thrombophilia should be considered an adverse factor in cases of embryo implantation failure which may present as unexplained infertility. Thrombophilia may be congenital or acquired and is related to changes in haemostatic mechanisms with increased risk of thromboembolism also. In general, thrombophilia should be considered a multifactorial disorder and not as an expression of a single genetic abnormality.[7] The relationship between thrombophilic factors and infertility should be taken into consideration because of the possibility of alterations in haemostasis of a thrombophilic nature at the implantation site. This vascular change affects trophoblast invasion and placental vasculature, hampering implantation of the embryo. The cause of unexplained infertility needs to be assessed more thoroughly so that we can treat more and more cases with specific treatment. If we can find out the cause more specific treatment can be provided and pregnancy rate can be improved. So far there have been very few studies conducted to find out the association of unexplained infertility with congenital thrombophilia so we conducted this study. Congenital factors suspected of being responsible for propensity for thrombosis include protein C, Protein S, Activated protein C resistance (APCR). Also, a great proportion of theses are due to factor V Leiden mutation. Increased homocystein levels may be acquired or genetic. Genetic may manifest due to Methylene tetrahydrofolatereductase (MTHFR) gene mutation, Antithrombin 111 and Prothrombin 20210 gene mutation. The aims of this study was to screen for congenital thrombophilia in unexplained infertility, and compare the incidence of thrombophilia with fertile female population to find whether it is one of the possible causes of unexplained infertility and if it is so, to determine the type of thrombophilia more prevalent in unexplained infertility.

METHODOLOGY

Study was conducted at All India Institute of Medical Sciences, New Delhi, India. After ethical clearance which was obtained from the Ethics Committee of the institute. Patients were recruited from the out-patient clinic after confirming the diagnosis of unexplained infertility. Informed written consent was taken after explaining the detailed plan and purpose of the study in their own language. Study group (Group A) comprised of 40 infertile patients of age between 20-40 years in whom no cause of infertility was identified. The women with male factor infertility, tubal, ovarian, uterine factors like PCOD, tubal block, tubercular endometritis contributing to infertility and history of thrombosis were excluded. The control group comprised of 40 healthy women with proven fertility, matched for age, with no history of thrombo-embolic events, who had conceived spontaneously and had at least one uneventful pregnancy, without any complication (such as preeclampsia, intrauterine growth restriction and intrauterine fetal death).

On enrollment a detailed clinical history including menstrual history, obstetric history and medical history was taken. Detailed examination including general physical examination and gynaecological examination was done. Baseline blood investigations like hemoglobin, VDRL, HIV, HBsAg, blood sugar-fasting/post prandial, thyroid stimulating hormone, prolactin, day-2 follicle stimulatinghormone (FSH), leutinising hormone (LH), estradiol, AMH (Anti-Mullerian

Hormone), husband semen Analysis (HSA) and a day-2 antral follicle count (AFC) were done. An ultrasound pelvis for accessing endometrium and ovaries, hysterosalpingogram for tubal status, and diagnostic laparoscopy-hysteroscopy were performed in all patients, before labeling them as unexplained infertility.

After proper selection of participants and informed consent, blood samples were collected for testing of congenital thrombophilic factors. Tests for inherited thrombophilia included Protein C, Protein S, Anti-thrombin III (Functional assay), Activated Protein C Resistance, serum Homocysteine, factor V Leiden (PCR), Prothrombin G20210 G (PCR) gene and MTHFR gene mutation, were done in both the groups. Protein C and Protein S are sandwich ELISA based tests, and Protein C and Protein S relative percent concentrations were determined against a curve prepared from the reference plasma provided with the kit. Anti-thrombin III is a chromogenic test. Activated Protein C Resistance is a plasma-based functional clotting assay. Factor V Leiden analysis was done if APCR was found to be low. Prothrombin 20210 was tested if Antithrombin was found to be lower to check point. And MTHFR gene was analysed in cases with higher homocysteine levels.

The primary outcome variables included incidence of congenital thrombophilia in unexplained thrombophilia and its comparison with control fertile female population and the frequency of congenital thrombophilia in the unexplained infertile population.

Mutation study of FVL, MTHFR and PT gene by PCR-RFLP method:

Genomic DNA was extracted from peripheral blood leukocytes by standard phenol chloroform methods. DNA amplification for FV Leiden, prothombin 20210G/A and MTHFR 677C/T was performed separately as individual PCR. Polymerase chain reaction was performed on PCR mixture containing total volume of 25µl that contained 200 ng DNA, 0.2 mmol/L of each of the deoxynucleotide triphosphate; 25 pmol of each oligonucleotide primer, each forward and reverse, reaction buffer (giving final concentration of 10 mmol/L, Tris-HCL, 50 mmol/L KCL, 1.5mmol/L $MgCl_2$, and 0.05% gelatin); and 1 U Taq polymerase. The PCR conditions were common for all the above PCRs. The conditions were 95^0 C for 5 minutes followed by 30 cycles at 95^0 C for 1 minute, 55^0C for 1 minute, and 72^0C for 10 minutes.

Statistical Analysis

Categorical variables were presented in number and percentage (%) and continuous variables were presented as mean ± SD and median. Normality of data was tested by Kolmogorov-Smirnov test. If the normality was rejected then non parametric test was used. Quantitative variables were compared using Unpaired t-test/Mann-Whitney Test and qualitative variables were compared using Chi-Square test /Fisher's exact test. Odds ratio with 95% confidence intervals calculated for selected variables and their significance tested. A p value of <0.05 was considered statistically significant. The data was entered in MS EXCEL spreadsheet and analysis was done using Statistical Package for Social Sciences (SPSS) version 21.0.

RESULTS

This is a cross-sectional study conducted to evaluate the incidence of congenital thrombophilia in unexplained infertility and to compare its incidence with the normal fertile population. A total of 40 participants were taken in the unexplained infertility group and 40 controls were taken. Participants in the control group were healthy females who had being borne at least one child.

The demographic profile was comparable in the two groups. The mean age of participants, BMI, mean FSH The mean prolactin, mean TSH level, mean E2 levels, mean AMH level were comparable in the unexplained infertility and control group (table 1)

Table 1: Comparison of demographic features in Unexplained Infertility Group and Control group

Demographic details	Group 1 (Unexplained Infertility)	Group 2 (Control)	P-value
Age[a]	29.4 +/- 3.04	28.52+/-3.18	0.09
Height[a]	160.25+/-3.36	160.28+/-3.25	0.992
BMI[a]	22.6+/-1.41	23.47	0.132
Hemoglobin[a]	11.59+/-0.97	11.06+/-1.02	0.12
Fasting blood sugar[a]	91.3+/-11.89	109.72+/-15.75	0.06
TSH[a]	2.57+/-1.02	2.45+/-0.91	0.985
FSH[a]	5.8+/-1.4	5.61+/-1.13	0.504
LH[a]	4.95+/-1.44	5.04+/-2.25	0.661
PRL[a]	13.99+/-2.75	15.26+/-2.2	*0.01*
E2[a]	90.64+/-17.91	92.13+/-12.17	0.743
AMH[a]	3.54+/-1.26	4.1+/-0.9	*0.026*
Day 2 AFC	9	8	0.186

a = mean ± Standard Deviation, b = median (maximum-minimum)

There were four (10%) patients in the unexplained infertility group (A) and one (2.5%) patient in the control group with low protein S. (p value-0.199). There were three (7.5%) patients with low Protein C in the infertility group and one (2.5%) in the control group (p value-0.328).

It was found that there were four (10%) subjects with low antithrombin levels in the infertility group and none in the control group. (p value- 0.127). Prothrombin gene mutation was studied in the four subjects who had low levels of Antithrombin III and it was found that two of them tested positive for the Prothrombin gene in study group.

It was found in this study that there were two (5%) cases with low APCR levels in the infertile population and two (5%) women with low APCR levels in the control population. (p value-1.000). Factor V Leiden mutation analysis was done for the four cases with low APCR levels and it was found that all four (two in study and two in control) tested positive for mutation (p value-1.000). All four were heterozygous for the mutation. Three (7.5%) cases from study group were reported to have high homocysteine levels and in the control population, one (2.5%) had high homocysteine level (p value-0.651). MTHFR mutation was tested in four cases with high homocysteinelevels ,3(all from the study group) were found positive for the mutation. Incidence of various inherited thrombophilia component in both groups are depicted in table 2

Table 2: Frequency of deficiency of thrombophilia factors in Unexplained Infertility group and Control group

	Unexplained Infertility N=40, no (%)	Control Group N=40, no (%)	P-value	Odds ratio	95% CI
Protein S	4 (10)	1 (2.5)	0.199	4.333	0.4624-40.6101
Protein C	3 (7.5)	1 (2.5)	0.328	3.162	0.3147-31.7768
Antithrombin III	4 (10)	0 (0)	0.127	9.986	0.5196-191.9154
Homocysteine	3 (7.5)	1/40 (2.5) 39/40 (97.5)	0.328	3.162	0.3147-31.7768
Activated Protein C resistance	2 (5)	2 (5)	1.000	1.000	0.1339-7.4702
Factor V Leiden Mutation	2 (5)	2/(5)	1.000	1.000	0.1339-7.4702
Prothrombin Gene Mutation (in Antithrombin III deficiency)	2 (2.5)	0 (0)	0.289	5.260	0.2446-113.1126
MTHFR Mutation (In cases with high homocysteine)	3 (7.5)	0 (0)	0.186	7.560	0.3778-151.293

Though, individually thrombophilic factors were not found to be significantly different in two groups, when a combined analysis was done, it was found that study group had significantly more thrombophilia cases. In the study group, there were 23 thrombophilia screen positives components whereas only seven abnormal thrombophilia factors were detected in 5 cases in control (p value-0.005). It was found that out of 23 positive thrombophilia factors in 14 cases in group 1, Protein S (10%) and Antithrombin III (10%) had the highest frequency followed by Homocysteine (7.5%), Protein C (7.5%), MTHFR gene mutation (7.5%), prothrombin 20210 (5%), Factor V Leiden (5%) and APCR (5%). Out of the seven positive thrombophilia cases in the control population, Factor V Leiden mutation and APCR had the highest frequency (5%) followed by Protein S, Protein C, and Homocysteine (2.5%); whereas, there were no cases of Anti-thrombin III and so Prothrombin 20210, and MTHFR gene. Overall there were 14 (35%) subjects in the unexplained infertility group with thrombophilic factor positive and 5 (12.5%) in the control group with positive thrombophilic factor (p value-0.023).

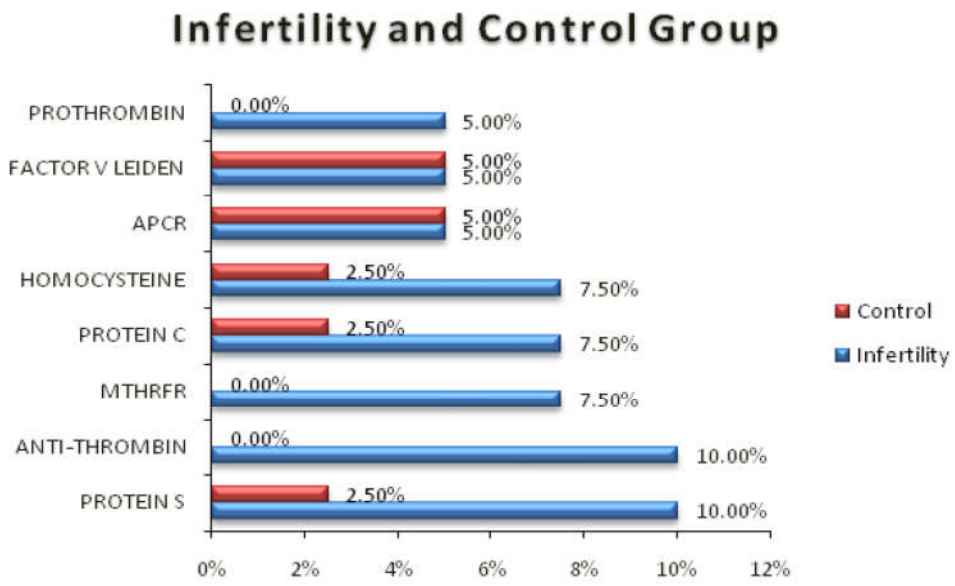


Fig 1: Graph showing the frequency of different Thrombophilias in the Unexplained Infertility group

In the study group, 5 cases had single factor deficiency/derangement; whereas, 7 cases had two and 2 cases had three factors deranged/ deficinet. In the control group, there were two patients with combined thrombophilias (two thrombophilic abnormalities). One patient had Protein C deficiency with hyperhomocysteinemia and the other patient had Protein S deficiency with hyperhomocysteinemia. (Details of thrombophilia screen factors is outlined in table 3)

Table 3: No of total cases and various factors in both group

Thrombophlia	Unexplained Infertility group Cases 40, tests 209	Control group Cases 40, tests 203	P-value
Thrombophilia positive cases	14 (35%)	5 (12.5%)	0.023
Total thrombophilia factors	23 (12%)	7 (3.4%)	0.005
Combined factors	1 in 7, 2 in 5, 3 in 2	1 in 3, 2 in 2	-

Table 4: Combined thrombophilia prevelence

Total no of Thrombophilia Factors	Positive cases-unexplained infertility, n=14	Positive cases-Control group n=5
One factor	7 (50% of 35%)	3 (60% of 12%)
Two factors	5 (a, b, c)	2 (c)
Three factors	2 (d,e)	0

a. Hyperhomocysteinemia + MTHFR gene mutation (n=3)
b. Antithrombin 111 + Prothrombin gene mutation (n=2)
c. APCR deficiency + Factor V ladein mutation (n=2 in infertile and 2 in controls)
d. Low Protein S + Hyper- homocysteinaemia + MTHFR gene mutation (n+1)
e. Low Protein C + Hyper-homocysteinaemia + MTHFR gene mutation (n+1)

DISCUSSION

The association between thrombophilia and recurrent pregnancy loss or poor pregnancy outcome

is well known. It may act by impairing the initial vascularization process occurring at implantation, which is necessary for a successful pregnancy.[8-10] However, there are limited data on the association between thrombophilia, hereditary or acquired, with female infertility and IVF failure.[4,8,11] A possible connection between inherited thrombophilia and the etiology of infertility has been found in some studies.[12-15] Thrombosis in the placental vessels leads to hypo perfusion of the inter-villous space and may cause placentation failure.[16,17] Failures of implantation and early placentation of embryos in IVF may be caused by similar mechanisms. However, other mechanisms may be responsible too, like the damage of decidual or chorionic vessels, or reduction of trophoblast invasiveness.[18,19] This study aimed to find the prevalence of congenital thrombophilia in unexplained infertility and its comparison with normal fertile female population. We wanted to determine if inherited thrombophilia can be addressed as defect leading to unexplained infertility; hence, instead of expectant or empirical treatment, we can offer appropriate treatment to these cases of unexplained infertility to achieve more promising outcomes.

We found higher incidence of inherited thrombophilia in infertile females as compared to fertile ones (35% vs 12.5%); thus, nearly threefold higher incidence of inherited thrombophilias in unexplained infertility. (p=0.023) In our study, the prevalence of low Protein S in unexplained infertility group was 10% vs 2.5% in the control group. This was 4-fold higher than the normal population but was not statistically significant (p =0.199). Similar pattern was observed in Protein C deficiency; 7.5% and 2.5% in the unexplained infertility and control groups, respectively, (p-0.328). Comparable results are reported in previous trials. Azem et al found the incidence of low Protein S in the study group (8.9%), but none reported in the control group , but no participants in the either group had deficiency of Protein C.[8] Other studies have also found (Safdarian et al., Qublan) low Protein C (but statistically not significant) in the unexplained infertility a.

We found similar incidence of low APCR levels and Factor V Leiden mutation in both groups, as seen in various previous reports also (4,8,11,22), Hyperhomocysteinemia, and MTHFR gene mutation have also not been observed associated with infertility in some studies.[4,8,11,20,22,23] Whereas higher incidence of heterozygous Factor V Leiden, (p=0.001) and MTHFR C667T homozygous gene mutation (p=0.02) were found associated with unexplained infertility.[24] In another study, prothrombin gene G20210 was found associated with infertility as compared to fertile females (5.7% vs 2.1%)(p=0.04).[25] Some could not establishead higher prevalence of thrombophilia in unexplained infertility.[27]

In our study, there were 14 subjects in the Unexplained Infertility group and five in the control group with at least one positive thrombophilic factor (p value<0.023). There were a total of 23 positives factors in the unexplained Infertility group and seven in the control group (p value-0.005). In a study conducted by Safdarian et al. it was seen that the combine thrombophilia prevalence was 59 (61.5%) in the recurrent IVF failure group and 31 (32.5%) in the control group.[20] Qublan et al. conducted a study where they found that the prevalence of combined thrombophilia in the recurrent IVF failure group was 35.6%, which was similar to our study; and that in the control population was 4.4%, which was statistically significant.[21] So it can be stated that Inherited thrombophilia might play a role in early implantation failure of the embryo and may lead to undiagnosed pregnancy loss. These results may be extrapolated to unexplained infertility.

Most of the studies conducted till date have observed the incidence of congenital thrombophilia in Recurrent IVF failures cut very few studies have assessed prevalence of congenital thrombophilia in unexplained infertility. The results of the present study revealed a higher prevalence of inherited thrombophilia in the unexplained infertility women compared to normal fertile. Hence, it can be hypothesized that Inherited thrombophilia might play a role in the mechanism involved in early undiagnosed pregnancy loss which may be a cause for unexplained infertility also.

Overall, we observed that congenital thrombophilia is significantly more in infertile cases than normal females, and we could find strong association with Antithrombin III and prothrombin gene mutation. Hyperhomocysteinemia without MTHFR gene mutation is unlikely to lead to infertility, however if associated with MTHFR mutation (heterozygous or homozygous), it may be implicated for infertility. Factor V Leiden which were in 5% cases and heterozygous in both the groups, could not be considered as contributing factor for infertility.

Strength of present study is that it is one of the first study conducted in South Asia, to study the prevalence of Congenital Thrombophilia as a factor contributing to unexplained Infertility. The few studies, which have studied congenital thrombophilia, have not studied all the congenital

thrombophilia factors. They have only studied the DNA mutation factors, which are inherited and are a cause of thrombophilia. The limitation of the present study is the small sample size. A larger sample size would have helped in determining prevalence of the thrombophilias in a more precise manner. Another drawback is that no intervention was given for the factors, which had come out to be positive in the unexplained infertility group. An intervention would have helped to find out, whether a prophylactic treatment may aid in conception in women with unexplained infertility.

CONCLUSION

Inherited thrombophilia combined analysis showed increased association of unexplained infertility with thrombophilia. Evaluation of thrombophilias may be an additional evaluation, beside other basic evaluations in patients with unexplained infertility. Inherited thrombophilia may have a significant role in embryo implantation failure. wProspective randomized controlled interventional studies with large numbers are needed to prove this effect and determine the effect of thromboprophylaxis in such cases.

REFERENCES

1. Grandone E. Infertility and trombophilia.Thromb Res. 2005; 115(1):24-7.
2. Vaquero E, Lazzarin N, Caserta D, Valensise H, Baldi M, Moscarini M, Arduii D. Diagnostic evaluation of women experiencing repeated in vitro fertilization failure. Eur J GynecolReprodBiol 2006; 125(1):79-84
3. Glueck CJ, Awadalla S G, Philips H, Cameron D, Wang P, Fontaine RN. Polycistic ovary síndrome, infertility, familial trombophilia, recurrent loss of in vitro fertilized embryos, and miscarriage. Fertility and Sterility 2000; 74(2): 394-7.
4. Grandone E, Colaizzo D, Lo Bue A, Checola MG, Cittadini E, Margaglione M. Inherited thrombophilia and in vitro fertilization implantation failure. Fertility and Sterility 2001; 76 (1): 201-02.
5. Sarto A, Rocha M, Geller M, Capmany C, Martinez M, Quintans, Donaldson M, Pasqualini RS. Tratamiento con enoxaparinaadaptado a los programas de fertilidad en mujeres con abortorecurrente y trombofiliaMedicina (Buenos Aires) 2001; 61: 406-12.
6. Machac S, Lubusky M, Prochazka M, Streda R. Prevalence of inherited thrombophilia in patients with severe ovarian hyperstimulation syndrome. Biomed Pap Med FacUnivPalacky Olomouc Czech Repub. 2006; 150 (2): 289-92.
7. Buchholz T, Thaler CJ. Inherited thrombophilia: impact on human reproduction. Am J ReprodImmunol 2003; 50 (1): 20-32.
8. Azem F, Many A, Yovel I, Amit A, Lessing JB, Kupferminc MJ. Increased rates of trombophilia in women with repeated FIV failures. Human Reproduction 2004; 19 (2): 368-70.
9. Geva E, Amit A, Lerner-Geva L, Azem F, Yovel I, Lessing JB. Autoimmune disorders: another possible cause for in-vitro fertilization and embryo transfer failure. Hum Reprod1995; 10: 2560-2563.
10. Kujovich JL. Thrombophilia and pregnancy complications. Am J ObstetGynecol2004; 191: 412-424.
11. Martinelli I, Taioli E, Ragni G, Levi-Setti P, Passamonti SM, Battagliolo T, Lodigiani C, Mannucci PM. Embryo implantation after assisted reproductive procedures and maternal thrombophilia. Haematologica 2003; 88(7):789-93.
12. Lindhoff-Last E, Luxembourg B. Evidence-based indications for thrombophilia screening. VASA 2008;37:19–30.
13. Thaler CJ, Budiman H, Ruebsamen H, Nagel D, Lohse P. Effects of the common 677C > T mutation of the 5,10-methylenetetrahydrofolate reductase (MTHFR) gene on ovarian responsiveness to recombinant follicle-stimulating hormone. Am J ReprodImmunol 2006;55:251–8.
14. Hecht S, Pavlik R, Lohse P, Noss U, Friese K, Thaler CJ. Common 677C > T mutation of the 5,10-methylenetetrahydrofolate reductase gene affects follicular estradiol synthesis. FertilSteril 2009;91:56–61.
15. Bianca S,BarranoB,Cutuli N, Indaco L, Cataliotti A, Milana G, et al. Unexplained infertility and inherited thrombophilia. FertilSteril 2009;92.e4.
16. Kupferminc MJ, Eldor A, Steinman N, Many A, Bar-Am A, Jaffa A, et al. Increased frequency of genetic thrombophilia in women with complications of pregnancy. N Engl J Med 1999; 340: 9-13.
17. Rey E, Kahn SR, David M, Shrier I. Thrombophilic disorders and fetal loss: a meta-analysis. Lancet 2003; 361: 901-908
18. Mousa HA, Alfirevic1 Z. Do placental lesions reflect thrombophilia state in women with adverse pregnancy outcome? Hum Reprod2000; 15: 1830-1833.
19. Rand JH, Wu XX, Guller S, Scher J, Andree HA, Lockwood CJ. Antiphospholipid immunoglobulin G antibodies reduce annexin-V levels on syncytiotrophoblast apical membranes and in culture media of placental villi. Am J ObstetGynecol1997; 177: 918-923
20. Safdarian L, Najmi Z, Aleyasin A, etal.Recurrent IVF failure and hereditary thrombophilia. Iran J Reprod Med Vol. 12. No. 7. pp: 467-470, July 2014

21. Qublan HS, Eid SS, Ababneh HÁ, AmarinZO, Smadi AZ, Al- Khafaji FF, KhaderYS. Acquired and inherited thrombophilia: implication in recurrent IVF and embryo tranfer failure. Hum Reprod. 2006; 21(10): 2694-8.
22. Kallen CB, Arici A. Immune testing in fertility practice: truth or deception? CurrOpinObstetGynecol 2003;15:225-231.l. Hum Reprod 2001;16:2403–2410
23. Casadei L, Puca F, Privitera L, Zamaro V, Emidi E. Inherited thrombophilia in infertile women: implication in unexplain infertility. FertilSteril 2010; 94(2): 755-757.
24. Bianca S. Barrano B. Cutuli N. Indaco L. Cataliotti A. Milana G. et al. Unexplained infertility and inherited thrombophilia. FertilSteril. 2009; (e4): doi: 10.1016/j.fertnstert.2009.02. 007.
25. CinziaFatini, Fatini C, Conti L, Turillazzi N, Cechi E S, Romanuoli I, Melanini M N, Cozzi C, Abbati R, Noc I unexplained infertility association with inherited thrombophilia. J.Thromb res 2012 129(5) el 185-188
26. CasadiaL,Privilera L, Emide E. Inherited Thrombophilia in infertile women. FertilSteril 2010. 94(2)p755-757.

SUBSCRIPTION FORM

I want to renew/subscribe international class journal "**Indian Journal of Obstetrics and Gynecology**" of Red Flower Publication Pvt. Ltd.

Subscription Rates:
• Institutional: INR 10500/USD 820.31

Name and complete address (in capitals):_____

_____

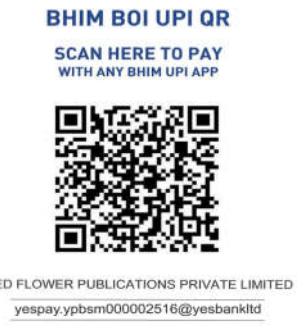
Payment detail:
Online payment link: http://rfppl.co.in/payment.php?mid=15

Cheque/DD: Please send the US dollar check from outside India and INR check from India made payable to 'Red Flower Publication Private Limited'. Drawn on Delhi branch.

Wire transfer/NEFT/RTGS:
Complete Bank Account No. 604320110000467
Beneficiary Name: Red Flower Publication Pvt. Ltd.
Bank & Branch Name: Bank of India; Mayur Vihar
MICR Code: 110013045
Branch Code: 6043
IFSC Code: BKID0006043 (used for RTGS and NEFT transactions)
Swift Code: BKIDINBBDOS

Term and condition for supply of journals
1. Advance payment required by Demand Draft payable to **Red Flower Publication Pvt. Ltd**. payable at **Delhi.**
2. Cancellation not allowed except for duplicate payment.
3. Agents allowed 12.5% discount.
4. Claim must be made within six months from issue date.

Mail all orders to
Subscription and Marketing Manager
Red Flower Publication Pvt. Ltd.
48/41-42, DSIDC, Pocket-II
Mayur Vihar Phase-I
Delhi - 110 091(India)
Phone: 91-11-79695648
Cell: +91-9821671871
E-mail: sales@rfppl.co.in



Case Report

Indian Journal of Obstetrics and Gynecology
Volume 12 Number 2, April – June 2024
DOI: http://dx.doi.org/10.21088/ijog.2321.1636.12224.6

A Large Gartner Cyst in an Unmarried 17 Years old Female: A Case Report

Nalini Sharma[1], Yapi Marging[2], Ahanthem Santa Singh[3], Dimple Kharkongor[4], Khulakpam Rimabati[5]

How to cite this article:
Nalini Sharma, Yapi Marging, Ahanthem Santa Singh *et al.* A Large Gartner Cyst in an unmarried 17 years old female: A Case Report. Indian J Obstet Gynecol. 2024;12(2):87-89.

ABSTRACT

In females during the phase of embryonic development the mesonephric ducts also known as wolffian ducts usually degenerate although it can be a persistent remnants which may become clinically apparent. This remnant of vestiges which can persist is called as Gartner duct. Gartner ducts generally are located in the proximal anterolateral wall of vagina, however it can be found at other sites along the vaginal length. It can be confused with other vaginal cysts like skenes cysts, epidermoid cysts, inclusion cyst, sebaceuous cyst, urethral diverticula. Mostly found fortuitously within the lateral vaginal wall during routine examination as Gartner cyst are mostly asymptomatic presentation clinically. Even so the patient present with Symptoms the complaints could include dyspareunia, vaginal pain, and difficulty inserting tampoons with associated vaginal infections. The gartner cyst has low columnar epithelium which secretes mucinous material, when the duct is blocked or occluded it gets collected which forms the cyst thereby during vaginal examination usually a tense cyst is palpable or seen to bulge beneath the vaginal wall. The size and extension of the cyst can be confirmed by radiological imagings and later on by histopathological. In sympatomaticpatients marsupialization or excision of Gartner duct cysts are usually done.

Keywords: Gartner duct; Cyst; Vaginal mass; Surgical Excision.

Author's Affiliation: [1]Additional Professor, [2,4]Senior Resident, [3]Senior Professor and Head, [5]2nd Year Post Graduate, Department of Obstetrics and Gynecology, North Eastern Indira Gandhi Regional Institute of Health & Medical Sciences, Shillong 793018, Meghalaya, India.

Corresponding Author: Yapi Marging, Senior Resident, Department of Obstetrics and Gynecology, North Eastern Indira Gandhi Regional Institute of Health & Medical Sciences, Shillong 793018, Meghalaya, India.

E-mail: Yapimarging87099@gmail.com

Received on: 27.06.2024

Accepted on: 12.08.2024

INTRODUCTION

Talking about the early embryonic developmental phase irrespective of the whether male or female fetus, there are mainly two types of ducts in the urogenital system which later on develop into reproductive and urinary system namely the Wolffian and the Müllerian ducts. Around the eight weeks of embryogenesis the mullerian ducts unite to form uterus, cervix and upper vagina and on the other hand in a female fetus Wolffian ducts becomes a vestigial organ which may form into gartner cyst.[1] Most of the time gartner cyst is a asymptomatic which is found incidentally during per vaginal examination. It is usually located in the anterolateral wall of vagina. It generally presents as

single unilateral vaginal cyst. They are usually not palpable per vaginally with the size usually being less than <2 cm but can also present with the larger mass which can be around 15 cms. Besides gartner duct cyst in vagina there are common vaginal cysts and mass presentations such as epidermal inclusion cyst, Bartholin duct cyst, and Mullerian cyst, Skene's gland cysts, urethral diverticulum, endometriotic cysts, and pelvic organ prolapse, particularly cystocele and enterocele.[2,3] Therefore It should be differentiated from other mass presentations in the vagina by clinical presentations, vaginal examinations, radiological examinations, and ultimately confirmed by histopathological findings. It is not uncommon that the benign cystic lesions of the urogenital tract can be seen in gynecologic and urologic practices. We are presenting a case report on a large gartner duct cyst in a 17 years unmarried girl who presented with a mass protruding out per vaginum and intraoperatively the mass was approximately 7×4×5 cm size in maximum dimension.[4]

CASE DESCRIPTION

A case of 17 yrs old unmarried nulligravida presented at gynaeopd with chief complain of swelling in genital tract which was insidious in onset and dysmenorrhea since menarche with history of analgesic intake to relieved the pain. No other associated known co-morbidities seen. Patient was not sexually active. Her menstrual cycle was regular lasting for 6-7 days, changes 2 to 3 pads per daywithout passage of any clots however with dysmenorrhea since menarche.

On local examination inspite of the cyst being large in size only small part of the cyst was seen protruding out of the introitusand it was palpable more at suprapubically.

USG whole abdomen was done on with normal size uterus and ET of 1.5 cm and a gartner cyst measuring 7.34×2.24×3.37 cm (shown in Fig. 1 A-C) in size at the right anterolateral wall of vagina. Bilateral adnexa were free with some free fluid in pod and no lymphadenopathy. CEMRI pelvis was done and it showed a non-enhancing suprapubic cystic lesion in right anterolateral wall of vagina.

During operation a gartner duct cyst of 7×4×5cm at right anterolateral of vaginal wall was seen. Open gartner cystectomy (shown in Fig. 2 A & B) was done by giving a transverse incision on the cyst over the anterior vaginal wall. Redundant vaginal wall excised n followed by a continuous sutures with vicryl 2'0. Betadine soaked roller gauge kept in situ.

Her post operative vitals were within normal range. The recovery period following the surgery went smoothly without any complications. The histopathological examination (as shown in Fig. 3 A & B) revealed that the cyst was lined with cuboidal and low columnar epithelium, lacking mucinous formation, and had a smooth muscle layer in the basal membrane, which is indicative of a Gartner duct cyst. She was discharged with a week and was heamodynamically stable all throughout the time and was advised to follow up. She visited at OPD for follow up after 3 weeks and with the wound all healed.

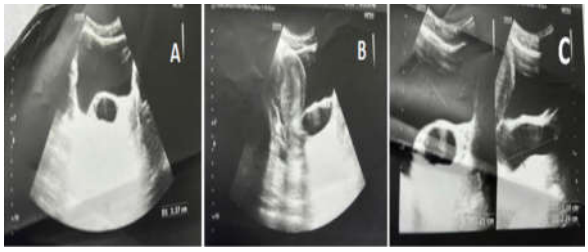


Fig. 1A-C: Ultrasound TAS image showing a well defined longitudinal cystic lesion of 7.34(CC)×2.24(AP)×3.37(TR) in anterior vaginal wall with most probability of being gartner duct cyst

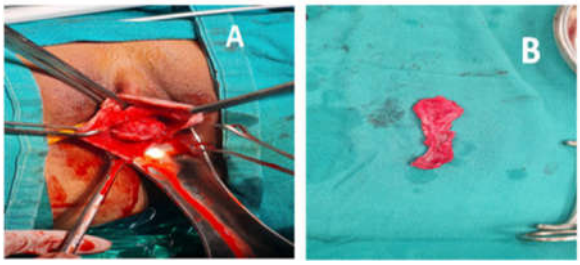


Fig. 2 A-B: Intraoperatively 7×4×5cm gartner cyst removed

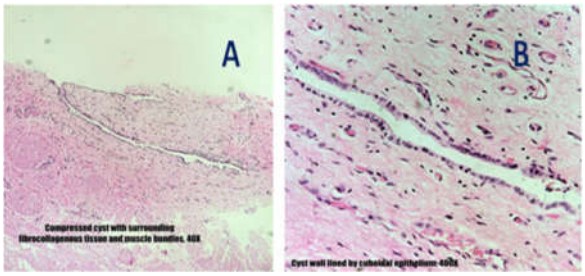


Fig. 3 A-B: A - showing cyst with fibrocollagenous tissue and muscle bundles on H&E at 40X magnification, B - cuboidal epithelium lining the cyst wall on H&E at 400X magnification

DISCUSSION

In female embryo, the wolffian (mesonephric) ducts typically regress, leaving the remnants such as the Gartner's duct, epoöphoron, and paroöphoron. If remnants of these ducts persist,

they can accumulate fluid, potentially leading to the formation of a vaginal wall cyst[5]. Vaginal cysts can be classified based on the histology of the cyst lining into three types: epidermal inclusion cysts, embryonic (Mullerian or Gartner's) cysts, and urothelial cysts.[6] It is usually seen in the reproductive age with approximate incidence of 1 in 200 female.[7] Gartner's duct cysts generally remain asymptomatic and are often discovered during a routine gynecological examination. However, in some cases it may enlarge to a noticeable size, that it not only cause symptoms such as visible skin tags but there can be urinary retention, pressure, itching, vaginal discharge dyspareunia (painful intercourse), pelvic pain, or a protrusion from the vagina so the gartner cyst can be confused with other mass presentation at the vagina.[8] Diagnosis can typically be achieved through a general vaginal examination and transvaginal ultrasound. While MRI can provide a more definitive diagnosis, it is usually not necessary in most cases. If the cysts are symptomatic and large, surgical excision or marsupilation is the primary treatment.[2,3,9]

CONCLUSION

For asymptomatic patients with Gartner's cysts, conservative therapy is a safe option due to the low incidence of these cysts. However, surgery is strongly recommended for patients experiencing severe symptoms or who have large cysts. During surgical intervention, it is an outmost important to insert a Foley catheter intraoperatively to prevent injuries to the urethra and bladder. Patients should be closely monitored after the procedure to minimize the risk of recurrence. A comprehensive clinical examination, along with radiological investigations not only to rule out the other causes of vaginal mass or cyst, is crucial for timely diagnosis and appropriate surgical management.

REFERENCES

1. Rios SS, Pereira LC, Santos CB, Chen AC, Chen JR, de Fátima B Vogt M. Conservative treatment and follow up of vaginal Gartner's duct cysts: a case series. J Med Case Rep. 2016;10:147. doi:10.1186/s13256-016-0936-1.
2. Sheih CP, Li YW, Liao YJ, Chiang CD. Small ureterocele-like Gartner's duct cyst associated with ipsilateral renal dysgenesis: report of two cases. J Clin Ultrasound. 1996 Nov-Dec;24(9):533-5. doi:10.1002/(SICI)1097-0096(199611/12)24:9<533::AID-JCU6>3.0.CO;2-1. [PubMed]
3. Department of Urology, University of Kansas Medical Center, Kansas City, KS, USA.
4. Inocencio G, Azevedo S, Braga A, Joao A. Large Gartner cyst. BMJ Case Rep. 2013;2013. doi:10.1136/bcr-2012-007996.
5. Vaginal cysts. (2023). Accessed: May 20, 2023: https://www.mountsinai.org/health-library/diseases-conditions/vaginal-cysts.
6. Pradhan S, Tobon H. Vaginal cysts: a clinicopathological study of 41 cases. Int J GynecolPathol. 1986;5(1):35-46.
7. Junaid TA, Thomas SM. Cysts of the vulva and vagina: a comparative study. Int J Gynaecol Obstet. 1981;19(3):239-43.
8. Letizia MJ, Kelly JV. Case report: gartner's duct cyst. Emerg Med News. 2011;33:35.
9. Akkawi R, Valente AL, Badawy SZA. Large mesonephric cyst with acute adnexal torsion in a teenage girl. J PediatrAdolesc Gynecol. 2012;25(6):143-5. doi:10.1016/j.jpag.2012.09.004. [PubMed]

SUBSCRIPTION FORM

I want to renew/subscribe international class journal "**Indian Journal of Obstetrics and Gynecology**" of Red Flower Publication Pvt. Ltd.

Subscription Rates:
- Institutional: INR 10500/USD 820.31

Name and complete address (in capitals):_____

_____

Payment detail:
Online payment link: http://rfppl.co.in/payment.php?mid=15

Cheque/DD: Please send the US dollar check from outside India and INR check from India made payable to 'Red Flower Publication Private Limited'. Drawn on Delhi branch.

Wire transfer/NEFT/RTGS:
Complete Bank Account No. 604320110000467
Beneficiary Name: Red Flower Publication Pvt. Ltd.
Bank & Branch Name: Bank of India; Mayur Vihar
MICR Code: 110013045
Branch Code: 6043
IFSC Code: BKID0006043 (used for RTGS and NEFT transactions)
Swift Code: BKIDINBBDOS

Term and condition for supply of journals
1. Advance payment required by Demand Draft payable to **Red Flower Publication Pvt. Ltd**. payable at **Delhi.**
2. Cancellation not allowed except for duplicate payment.
3. Agents allowed 12.5% discount.
4. Claim must be made within six months from issue date.

Mail all orders to
Subscription and Marketing Manager
Red Flower Publication Pvt. Ltd.
48/41-42, DSIDC, Pocket-II
Mayur Vihar Phase-I
Delhi - 110 091(India)
Phone: 91-11-79695648
Cell: +91-9821671871
E-mail: sales@rfppl.co.in

Case Report

Indian Journal of Obstetrics and Gynecology
Volume 12 Number 2, April – June 2024
DOI: http://dx.doi.org/10.21088/ijog.2321.1636.12224.7

Recent Updates on Carcinosarcoma of the Uterus

Priyanka Yoga. Purini[1], Sharmila V[2], Abhishek Raghava K S[3], Poongodi R[4], Darshan H.N[5]

How to cite this article:

Priyanka Yoga. Purini, Sharmila V, Abhishek Raghava K S *et al*. Recent Updates on Carcinosarcoma of the Uterus. Indian J Obstet Gynecol. 2024;12(2):91-94.

Abstract

Carcinosarcoma is a very rare, aggressive malignant neoplasm of the uterus and it is associated with poor prognosis. We are presenting a case of a 66-year-old multiparous postmenopausal women who had bleeding for a period of 3 months. On MRI Imaging there is a 6 cm lesion in the endometrial cavity, biopsy from the endometrium showed carcinosarcoma and she underwent extrafascial hysterectomy with bilateral slapingoophorectomy, omentectomy, and retroperitoneal lymph node dissection. Postoperatively ascites is positive for malignant cells, histopathology of specimen reported as carcinosarcoma FIGO grade 3 and lymph nodes are positive for malignancy. She received adjuvant chemotherapy with carboplatin and paclitaxel.

Keywords: Post menopausal bleeding; Polypoidal mass; Carcinosarcoma; Malignant mixed mullein tumour.

INTRODUCTION

Carcinisarcomas are very rare, aggressive in nature and associated with poor prognosis irrespective of the stage of disease, the survival rate is 50% even in the early stage of the disease.[1] Carcinosarcoma of uterus accounts for 2%-5% of uterine malignancies.[2] The World Health Organization (WHO) classification of uterine neoplasms, uterine malignancies containing both carcinomatous and sarcomatous elements are designated as carcinosarcoma. These neoplasms, also known as malignant mixed mullerian tumors, are usually seen among elderly postmenopausal women. These tumors are highly aggressive, and often present at an advanced stage, commonly FIGO III or IV. Uterine carcinosarcoma and endometrial carcinoma share similar risk factors, such as obesity, nulliparity, exogenous estrogen use, tamoxifen use. Oral contraceptive usage protects against the development of both. The sarcomatous component of these tumors may be either homologous (composed of tissues normally found in the uterus) or heterologous (containing tissues not normally found in the uterus, most commonly malignant cartilage or skeletal muscle). Most carcinosarcomas but not all, are monoclonal, derived from a single stem cell. The sarcomatous element is derived from the carcinomatous component by dedifferentiation.[3] Spread of carcinosarcomas is primarily via lymphatics like endometrial carcinomas, whereas true sarcomas, commonly metastasise hematogenously. The behavior of these tumors are determined by the epithelial component. Epithelial elements invade the lymphatic, vascular

Author's Affiliation: [1,3,4]Assistant Professor, Department of Obstetrics and Gynaecology, Department of Medical Oncology, Department of Pathology, [2]Professor and Head, Department of Obstetrics and Gynaecology, [5]Academic Junior Resident, Department of Obstetrics and Gynaecology, All India Institute of Medical Sciences, Mangalagiri 522503, Andhra Pradesh, India.

Corresponding Author: Priyanka Yoga. Purini, Assistant Professor, Department of Obstetrics and Gynaecology, All India Institute of Medical Sciences, Mangalagiri 522503, Andhra Pradesh, India.

E-mail: priyankapurini@gmail.com

Received on: 05.06.2024 **Accepted on:** 10.08.2024

spaces and metastasize, whereas the spindle cell component has a very limited metastatic potential.[1] Immunohistochemistry staining of uterine carcinosarcoma tissue shows expression of p27, p53, p16, c-KIT, COX-2, EGFR, HER2/neu, the oncogene AKT, the PIK3C gene, and the PAX8 paired genes.[4] Surgery is the main modality of treatment in carrionsarcoma of uterus. Extrafascial hysterectomy bilateral salpingoophorectomy with retroperitoneal lymph node dissection and omentectomy.[5] Pelvic lymph node dissection is advised in all stages of uterine carcinosarcoma.[4] Adjuvant chemotherapy with ifosfamide alone or in combination with platinum based drugs improves overall survival compared to adjuvant vaginal brachytherapy. Carboplatin and paclitaxel are another set of chemotherapeutic agents which have proven good survival outcomes.[4] Here we present a case of the carcinosarcoma of uterus successfully managed surgically, followed by adjuvant chemotherapy.

CASE REPORT

A 66-year-old postmenopausal woman presented to us with complaints of bleeding on and off for a period of 3 months. Her obstetric index was P3L3 with normal vaginal delivery, and she was tubectomised. She was a known case of diabetes and hypertension for 10 years. A history of transient ischemic attack 10 years ago for that she was taking only Aspirin. On examination, her vitals were stable. The abdominal examination was normal. Per speculum examination revealed approximately 2 cm x 1 cm mass protruding through the cervical os and the external os is seen as a rim around the polypoidal mass, and it is not bleeding on touch. Per vaginal examination also revealed the same findings: the cervix felt like a rim around the mass, and vaginal fornices were free of tumor. On rectal examination, rectal mucosa and bilateral parametrium are free of tumor. Endometrial and endocervical biopsy done at some other hospital is suggestive of endocervical adenocarcinoma, IHC positive for P16, P53 and negative for ER. She had been further evaluated at our institute, MRI imaging showed well-defined T1 hypo intense, T2 heterogenous lesion measuring 6.3×3.2 cm was noted distending the endometrial cavity and endocervical canal with myometrial shining, restriction on DW1 and corresponding low ADC value, the lesion showed heterogenous post contrast enhancement suggestive of Endometrial carcinoma. As there is a discrepancy between HPE and imaging, biopsy was done once again. Biopsy from the growth, endocervical and endometrial regions and HPE were suggestive of carcinosarcoma, probably endometrial origin. She underwent Extrafascial hysterectomy, bilateral salpingoophorectomy with omentectomy and retroperitoneal lymph node dissection. Intraoperatively she had minimal ascites which was sent for cytology, and was positive for malignant cells. Her postoperative period was uneventful. Macroscopically, the cut section of the uterus showed an expophytic growth grey-white-to-grey-brown-tumor measuring 4.5x5cm extending less than half of the myometrium. The rest of the specimen was normal. Microscopically, it was suggestive of carsinosarcoma FIGO grade 3, there was no cervical stromal invasion (Fig a, b). However, lymphovascular space invasion was present. Bilateral tubes, ovaries and momentum were unremarkable. Her pelvic lymph nodes were involved by a tumor. FIGO staging is stage IIIC. Further plan of management is discussed at our multidisciplinary tumor board and planned for adjuvant chemotherapy with carboplatin and paclitaxel for 6 cycles once in three weeks.

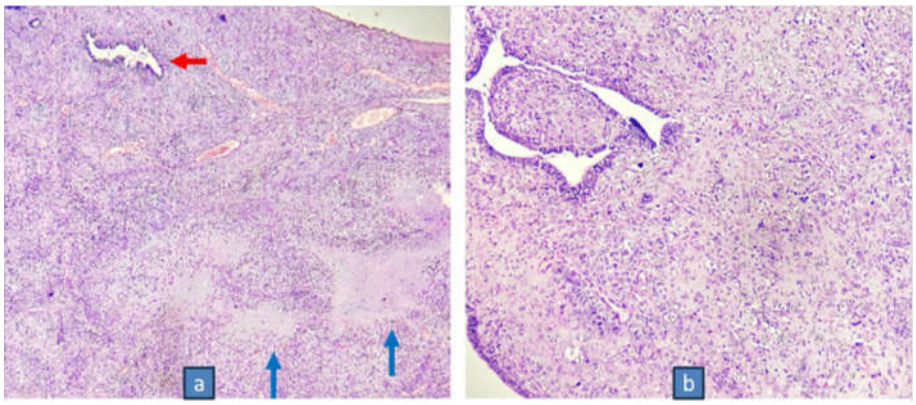


Fig. a: Microphotograph showing tumor with predominantly sarcomatous areas with cartilaginous matrix differentiation (blue arrows) and focal glandular differentiation (red arrow) (H&E, X40)

Fig. b: Microphotograph in higher power showing tumor with atypical glands and sheets of mesenchymal tumor cells (H&E, X400)

Brief Note

Histopathology slides revealed a tumor Composed of the glandular and mesenchymal differentiation. The glands are lined by atypical cells with minimal stratification and the mesenchymal areas are composed of sheets of polygonal to spindle shaped cells with focal cartilaginous differentiation (Fig. a, b).

DISCUSSION

Endometrial carcinosarcoma is a rare and aggressive high-grade endometrial carcinoma, accounting for 5% of all uterine malignancies and nearly 20% of non-endometrioid endometrial cancer. Endometrial carcinosarcoma is responsible for 15% of deaths from uterine malignancies.[6] Carcinosarcoma of the uterus is usually seen among postmenopausal women. The risk factors for carcinosarcoma includes pelvic exposure to irradiation, obesity, nulliparity, exposure to the human papillomavirus or exogenous estrogen, history of tamoxifen therapy, black race. These tumors are associated with a poor prognosis. Carcinosarcomas have a monoclonal origin from a common multidirectional progenitor stem cell. These neoplasms are derived from the Müllerian epithelium's single stem cells, which undergo metaplasia or dedifferentiation resulting in the sarcomatous elements.[7] It is diagnosed at an advanced stage more often compared to other endometrial cancers. The stage at diagnosis follows a bimodal distribution: 40–50% of cases are early stage (International Federation of Gynecology and Obstetrics ((FIGO) I–II) and 50–60% are advanced (FIGO III–IV). Up to 30–40% of patients present with lymph node metastases at diagnosis, and 10% have distant metastatic spread, especially in the lungs. Over 60% of patients with apparently early-stage disease at the time of initial diagnosis due to occult metastatic spread, these tumors are upstaged following comprehensive surgical evaluation. The prognosis remains poor despite the multimodal treatment strategy (surgery, platinum-based chemotherapy, radiotherapy). The median overall survival is less than 2 years, and the 5-year overall survival rate is less than 30% (about 50% and 20% in early and advanced stages, respectively). In early stage disease, the 5-year recurrence rate is 45% and 5-year related mortality of 50%. The average age of the patients at the time of diagnosis is 67 years.[7] The most common symptom of this malignancy is post-menopausal bleeding or spotting, discharge per vagina, abdominal pain and these are similar to endometrial adenocarcinoma. These tumors are a rapidly growing fleshy polypoidal mass protruding through the cervix into the vaginal canal. Diagnosis is made by biopsy from the endometrium or from the polypoidal mass. In this case, the age of the patient at the time of diagnosis is 66 years, presented with postmenopausal bleeding. On examination, a polypoid fleshy mass is seen through the cervical os protruding into the vaginal canal. Imaging techniques such as ultrasonography, CT scan of the abdomen and thorax or MRI of the pelvis are useful for staging and metastasis workup. Endometrial carcinosarcoma is now considered as a primary endometrial carcinoma, its treatment is similar to that of other nonendometrioid high-grade endometrial cancer, as per ESGO/ESTRO/ESP and the National Comprehensive Cancer Network (NCCN) guidelines.[8,9] The main stay of treatment is combined multimodal approach surgery, chemotherapy and/or radiotherapy. Surgical management is by extrafascial hysterectomy, bilateral salpingoophorectomy with retroperitoneal pelvic lymph node dissection with infracolicomentectomy. Peritoneal cytology is not mandatory as it is not a cancer staging factor, but it can be useful as a risk factor for tailoring the adjuvant treatment.[8,10] In our patient, sampling of endometrium and polypoidal mass revealed carcinosarcoma, and on further work up MRI is suggestive of endometrial carcinoma. Then she underwent hysterectomy with bilateral salipngoopherectomy, retroperitoneal lymph node dissection with infracolicomentectomy. Peritoneal cytology is positive for malignant cells. Histopathology of the hysterectomy specimen showed carciniosarcoma with lymph node metastasis. Based on the results from the GOG-232B and GOG-261 trials, it is recommended that carboplatin/paclitaxel doublet is the preferred first-line treatment for endometrial carcinosarcoma, given the non-inferiority and the better toxicity profile, compared with ifosfamide/paclitaxel. Based on the results of several trials, recently immunotherapy (with or without tyrosine kinase inhibitor) is emerging as the standard treatment modality after the failure of platinum-based chemotherapy. Pembrolizumab plus lenvatinib represents the preferred treatment for non-endometrioid endometrial cancer.

The majority of endometrial carcinosarcomas share molecular and genomic similarities with high-grade serous ovarian carcinoma and serous endometrial carcinoma, pmutations such as TP53 (60–97%), FBXW(10-44%), PPP2R1A(11-30%), HER2 (9–18%) serous-like mutations are common. Whereas the minority resembles the endometrioid

counterpart, such as ARID1A (10–25%), KRAS (8–15%), PTEN (10–50%), and PIK3CA (20–40%) are less frequent.[11] The analysis of The Cancer Genome Atlas (TCGA) Research Network and the Proactive Molecular risk classifier for Endometrial cancer (ProMisE) classification, four novel molecular endometrial cancer subgroups were identified.[12] The new classification includes POLE/ultramutated (POLE mutated), microsatellite- instable/ hypermutated (MSI-H), copy-number-high/ TP53-abnormal (P53-abn), and copy-number-low/ TP53-wild-type or non-specific molecular profile endometrial cancers. The TCGA study included only the endometrioid and serous histotypes, while limited data is known regarding less common endometrial cancer histotypes, such as endometrial carcinosarcoma.[13] A meta-analysis of four studies (231 patients) reported the pooled prevalence of the TCGA groups among endometrial carcinosarcomas 5.3% POLE, 7.3% MSI-H, 73.9% p53-abnormal, and 13.5% non-specific molecular profile. The majority of endometrial carcinosarcoma (73.9%) are classified within the serous like, p53-abn risk group (which accounts for 5–15% of endometrial cancers and resembles type II endometrial cancers). These tumors are characterized by advanced stage at diagnosis, late onset, mutant like/ abnormal p53 immunohistochemical staining, low mutational burden (<10 mutations per megabase), aggressive behavior, high risk of early relapse, and a dismal prognosis. POLE mutated endometrial carcinosarcoma showed an excellent prognosis similar to that of POLE mutated endometrioid endometrial cancers, supporting their inclusion in the same low-risk category for treatment purposes. On the other hand, the prognosis of p53-abn and non-specific molecular profile endometrial carcinosarcoma is worse than that of their endometrioid/serous counterparts.Where as MSI-H/dMMR tumors are unclear and remains to be clarified.[6]

REFERENCES

1. Anupama R, Kuriakose S, Vijaykumar DK, Pavithran K, Jojo A, Indu RN, Sheejamol VS. Carcinosarcoma of the uterus-a single institution retrospective analysis of the management and outcome and a brief review of literature. Indian J Surg Oncol. 2013 Sep;4(3): 222-8. doi: 10.1007/s13193-012-0206-7. Epub 2013 Jan 27. PMID: 24426726; PMCID: PMC3771046.
2. Adachi, Y., Nonogaki, H., Minamiguchi, S., Li, M., & Ikehara, S. (2016). Carcinosarcoma of the uterus: A case report. Molecular and Clinical Oncology, 4, 571-573. https://doi.org/10.3892/mco.2016.744.
3. McCluggage WG. Malignant biphasic uterine tumours: carcinosarcomas or metaplastic carcinomas? J Clin Pathol. 2002 May;55(5):321-5. doi: 10.1136/jcp.55.5.321. PMID: 11986333; PMCID: PMC1769650.
4. Menczer J. Review of Recommended Treatment of Uterine Carcinosarcoma. Curr Treat Options Oncol. 2015 Nov;16(11):53. doi: 10.1007/s11864-015-0370-4. PMID: 26374341.
5. Jaime Prat, 'Nomonde Mbatani Uterine sarcomas. International Journal of Gynecology & Obstetrics pages: S105-S110 Volume 131Issue S2 First Published online: 11 October 30, 2018 https://doi.org/10.1002/ijgo.12613.
6. Bogani G, Ray-Coquard I, Concin N, *et al*. Int J Gynecol Cancer 2023;33:147–174.
7. Tuan HX, Duc NM, Tri CM, Quyen HD, Dung PX. Carcinosarcoma of uterus. Radiol Case Rep. 2023 Jan 15;18(3):1297-1301. doi: 10.1016/j.radcr.2022.12.070. PMID: 36684637; PMCID: PMC9851838.
8. Concin N, Planchamp F, Abu-Rustum NR, *et al*. European Society of Gynaecological Oncology quality indicators for the surgical treatment of endometrial carcinoma. Int J Gynecol Cancer 2021;31:1508–29.
9. Abu-Rustum NR, Yashar CM, Bradley K, *et al*. NCCN Guidelines® insights: uterine neoplasms, version 3.2021. J Natl Compr Canc Netw 2021;19:888–95.
10. Matsuzaki S, Klar M, Matsuzaki S, *et al*. Uterine carcinosarcoma: contemporary clinical summary, molecular updates, and future research opportunity. Gynecol Oncol 2021;160:586–601.
11. Raffone A, Travaglino A, Raimondo D, *et al*. Uterine carcinosarcoma vs endometrial serous and clear cell carcinoma: a systematic review and meta-analysis of survival. Int J Gynaecol Obstet 2022;158:520–7.
12. Travaglino A, Raffone A, Raimondo D, *et al*. Prognostic value of the TCGA molecular classification in uterine carcinosarcoma. Int J Gynaecol Obstet 2022;158:13–20.
13. Cancer Genome Atlas Research Network, Kandoth C, Schultz N, *et al*. Integrated genomic characterization of endometrial carcinoma. Nature 2013;497:67–73.

Case Report

Indian Journal of Obstetrics and Gynecology
Volume 12 Number 2, April – June 2024
DOI: http://dx.doi.org/10.21088/ijog.2321.1636.12224.8

Case Report on Umbilical Cord Haemangioma: A Rare Entity

Shivani V. Bhandari[1], Vaishali S[2]. Taralekar, Apoorva J. Girme[3]

How to cite this article:
Shivani V. Bhandari, Vaishali S. Taralekar, Apoorva J. Girme. Case Report on Umbilical Cord Haemangioma: A Rare Entity. Indian J Obstet Gynecol. 2024;12(2):95-96.

Abstract

Many structural abnormalities of the umbilical cord can be identified with the aid of ultrasonography in the antenatal period. The umbilical cord contains two arteries and one vein surrounded by a gelatinous stroma (i.e., Wharton's jelly) and covered by a single layer of amnion. Umbilical cord, allows for the transfer of oxygen and nutrients from the maternal circulation into fetal circulation while simultaneously removing waste products.

Haemangiomas are common benign neoplasms arising from endothelial cells which typically takes place in the skin and soft tissues. Umbilical cord hemangiomas consist of an angiomatous nodule containing and encompassed by edema and myxomatous degeneration of Wharton's jelly, often cystic. Prenatal sonographic differentiation between cord hemangioma and hematoma can be difficult but is possible, Doppler can allow visualization of the vascular architecture within a hemangioma, while a hematoma does not have internal blood flow.

We report a case of, a 20 yr old Primigravida with 37 weeks 5 days pregnancy with intra uterine fetal demise with umbilical cord haemangioma.

Keywords: Umbilical cord haemangioma; Intra uterine fetal demise.

INTRODUCTION

Haemangiomas are common benign neoplasms arising from endothelial cells. They typically take place in the skin and soft tissues. However, they can affect all organs. Several hundred cases of placental haemangiomas are reported in the literature. However, the umbilical cord is extremely unusual as a site of occurrence.[1]

Author's Affiliation: [1]Resident, [2]Professor, [3]Assistant Professor, Department of Obstetrics and Gynaecology, Bharati Hospital and Research Center, Pune 411043, Maharashtra India.

Corresponding Author: Vaishali S. Taralekar, Professor, Department of Obstetrics and Gynaecology, Bharati Hospital and Research Center, Pune 411043, Maharashtra India.

E-mail: vaishutaralekar@gmail.com

Received on: 19.06.2024

Accepted on: 05.08.2024

CASE REPORT

A 20 year old, Primigravida with 37 weeks 5 days pregnancy came with complaints of absent fetal movements since 1 day, with no signs of labour. On her abdomen examination, fetal heart sounds not found and ultrasound was suggestive of intra uterine fetal demise.

Her last menstrual period was on 05.08.2023 with regular menstrual cycles. Her antenatal period was uneventful till 32 weeks of gestation, where her routine ultra sound detected umbilical cord haemangioma, there was a long segment of umbilical cord close to the abdominal wall insertion measuring more than 8 cm. this segment had excess of Wharton's jelly, rest of the cord appeared normal. The umbilical vein is dilated with diameter of more than 9 mm and the dilatation of the umbilical vein appeared to be related to the dilated cord. Placenta appeared to be normal, along with normal Doppler findings. Detailed counselling of patient and relatives was done regarding the condition, and advised weekly follow up. But patient did

not follow up with her visits and reported to the hospital with above said complaints at 37 weeks 5 days.

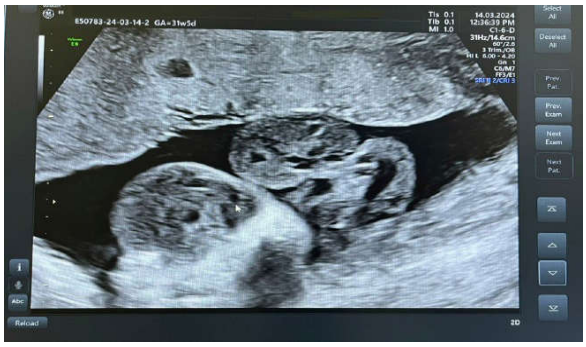


Fig. 1: The above ultrasonographic image shows dilated umbilical cord with excess of Wharton's jelly

After diagnosis of intra uterine fetal demise at 37 weeks 5 days pregnancy, patient was admitted and induction of labour was done by intracervical instillation of cerviprime gel. After 16 hours of labour, she delivered a male child of 2.6 kg uneventfully. Post delivery, the umbilical cord examined showed findings consistent with haemangioma, and placenta was found to be morphologically normal.

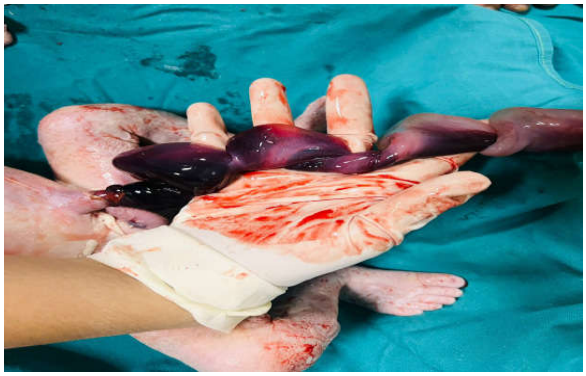


Fig. 2: The above images depicts umbilical cord haemangioma post delivery

Patient had an uneventful post delivery period and was discharged on 2nd post natal day. Histopathology reports were consistent with umbilical cord haemangioma with normal placenta.

DISCUSSION

Haemangioma is rare benign anomaly of umbilical cord arising from allantoic or omphalomesenteric vessels.

It is generally located in distal part of cord, and can be easily misdiagnosed. Thus, careful antenatal evaluation is necessary for early detection which helps in reducing perinatal morbidity and mortality. The differential diagnosis includes umbilical cord teratoma, aneurysm, haematoma and omphalomesenteric duct cyst.

Antenatal diagnosis of umbilical cord haemangioma is confirmed post delivery, by histopathology. In previous studies, elevated alpha feto protein levels are associated with increased risk of umbilical cord haemangioma.[2]

Wharton's jelly area as depicted by prenatal ultrasound correlates with the functional capacity of the placenta and thus merits further evaluation with currently available tests of placental function in clinical practice.[3]

Gross pathology assessment depicts a fusiform-shaped swelling of the umbilical cord engulfed by edema of adjacent Wharton's jelly. This condition carries a high morbidity and mortality rate of approximately 35%, often related to coexisting factors, nonimmune hydrops, polyhydramnios, fetal disseminated intravascular coagulopathy (DIC), fetal growth restriction, additional haemangiomas, other fetal anomalies, and stillbirth. Stillbirth may result secondary to mechanical obstruction of umbilical vessels by the tumour.[3]

CONCLUSION

Umbilical cord haemangioma is a rare entity, which requires close antenatal monitoring, as it is associated with high perinatal morbidity and mortality. In our case, as the patient did not follow up as advised, it resulted in a poor outcome of the fetus.

REFERENCES

1. Angelico G, Spadola S, Ieni A, et al. Hemangioma of the umbilical cord with associated amnionic inclusion cyst: two uncommon entities occurring simultaneously. *Pathologica*. 2019; 111(1): 13-17.
2. Yakıştıran B, ÇelenŞ, AksakalUsluA. Hemangioma of the umbilical cord: a case report. Adv Res ObstetGynaecol. 2023;1(1):e2303.
3. Sherer, D. M., Al-Haddad, S., Cheng, R., & Dalloul, M. (2021). Current Perspectives of Prenatal Sonography of Umbilical Cord Morphology. *International Journal of Women's Health*, *13*, 939–971.

SUBSCRIPTION FORM

I want to renew/subscribe international class journal "**Indian Journal of Obstetrics and Gynecology**" of Red Flower Publication Pvt. Ltd.

Subscription Rates:
- Institutional: INR 10500/USD 820.31

Name and complete address (in capitals):_____

_____

Payment detail:
Online payment link: http://rfppl.co.in/payment.php?mid=15

Cheque/DD: Please send the US dollar check from outside India and INR check from India made payable to 'Red Flower Publication Private Limited'. Drawn on Delhi branch.

Wire transfer/NEFT/RTGS:
Complete Bank Account No. 604320110000467
Beneficiary Name: Red Flower Publication Pvt. Ltd.
Bank & Branch Name: Bank of India; Mayur Vihar
MICR Code: 110013045
Branch Code: 6043
IFSC Code: BKID0006043 (used for RTGS and NEFT transactions)
Swift Code: BKIDINBBDOS

Term and condition for supply of journals
1. Advance payment required by Demand Draft payable to **Red Flower Publication Pvt. Ltd**. payable at **Delhi.**
2. Cancellation not allowed except for duplicate payment.
3. Agents allowed 12.5% discount.
4. Claim must be made within six months from issue date.

Mail all orders to
Subscription and Marketing Manager
Red Flower Publication Pvt. Ltd.
48/41-42, DSIDC, Pocket-II
Mayur Vihar Phase-I
Delhi - 110 091(India)
Phone: 91-11-79695648
Cell: +91-9821671871
E-mail: sales@rfppl.co.in

Guidelines for Authors

Manuscripts must be prepared in accordance with "Uniform requirements for Manuscripts submitted to Biomedical Journal" developed by international committee of medical Journal Editors

Types of Manuscripts and Limits

Original articles: Up to 3000 words excluding references and abstract and up to 10 references.

Review articles: Up to 2500 words excluding references and abstract and up to 10 references.

Case reports: Up to 1000 words excluding references and abstract and up to 10 references.

Online Submission of the Manuscripts

Articles can also be submitted online from http://rfppl.co.in/customer_index.php.

I) First Page File: Prepare the title page, covering letter, acknowledgement, etc. using a word processor program. All information which can reveal your identity should be here. use text/rtf/doc/PDF files. Do not zip the files.

2) Article file: The main text of the article, beginning from Abstract till References (including tables) should be in this file. Do not include any information (such as acknowledgement, your name in page headers, etc.) in this file. Use text/rtf/doc/PDF files. Do not zip the files. Limit the file size to 400 Kb. Do not incorporate images in the file. If file size is large, graphs can be submitted as images separately without incorporating them in the article file to reduce the size of the file.

3) Images: Submit good quality color images. Each image should be less than 100 Kb in size. Size of the image can be reduced by decreasing the actual height and width of the images (keep up to 400 pixels or 3 inches). All image formats (jpeg, tiff, gif, bmp, png, eps etc.) are acceptable; jpeg is most suitable.

Legends: Legends for the Fig.s/images should be included at the end of the article file.

If the manuscript is submitted online, the contributors' form and copyright transfer form has to be submitted in original with the signatures of all the contributors within two weeks from submission. Hard copies of the images (3 sets), for articles submitted online, should be sent to the journal office at the time of submission of a revised manuscript. Editorial office: Red Flower Publication Pvt. Ltd., 48/41-42, DSIDC, Pocket-II, Mayur Vihar Phase-I, Delhi – 110 091, India, Phone: 91-11-79695648, Cell: +91-9821671871. E-mail: author@rfppl.co.in. Submission page: http://rfppl.co.in/article_submission_system.php?mid=5.

Preparation of the Manuscript

The text of observational and experimental articles should be divided into sections with the headings: Introduction, Methods, Results, Discussion, References, Tables, Fig.s, Fig. legends, and Acknowledgment. Do not make subheadings in these sections.

Title Page

The title page should carry

1) Type of manuscript (e.g. Original article, Review article, Case Report)
2) The title of the article should be concise and informative;
3) Running title or short title not more than 50 characters;
4) The name by which each contributor is known (Last name, First name and initials of middle name), with his or her highest academic degree(s) and institutional affiliation;
5) The name of the department(s) and institution(s) to which the work should be attributed;
6) The name, address, phone numbers, facsimile numbers and e-mail address of the contributor responsible for correspondence about the manuscript; should be mentoined.
7) The total number of pages, total number of photographs and word counts separately for abstract and for the text (excluding the references and abstract);
8) Source(s) of support in the form of grants, equipment, drugs, or all of these;
9) Acknowledgement, if any; and
l0) If the manuscript was presented as part at a meeting, the organization, place, and exact date on which it was read.

Abstract Page

The second page should carry the full title of the manuscript and an abstract (of no more than 150 words for case reports, brief reports and 250 words for original articles). The abstract should be structured and state the Context (Background), Aims, Settings and Design, Methods and Materials, Statistical analysis used, Results and Conclusions. Below the abstract should provide 3 to 10 keywords.

Introduction

State the background of the study and purpose of the study and summarize the rationale for the study or observation.

Methods

The methods section should include only information that was available at the time the plan or protocol for the study was written such as study approach, design, type of sample, sample size, sampling technique, setting of the study, description of data collection tools and methods; all information obtained during the conduct of the study belongs in the Results section.

Reports of randomized clinical trials should be based on the CONSORT Statement (http:// www. consort-statement. org). When reporting experiments on human subjects, indicate whether the procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional or regional) and with the Helsinki Declaration of 1975, as revised in 2000 (available at http://www.wma. net/e/policy/l 7-c_e.html).

Results

Present your results in logical sequence in the text, tables, and illustrations, giving the main or most important findings first. Do not repeat in the text all the data in the tables or illustrations; emphasize or summarize only important observations. Extra or supplementary materials and technical details can be placed in an appendix where it will be accessible but will not interrupt the flow of the text; alternatively, it can be published only in the electronic version of the journal.

Discussion

Include summary of key findings (primary outcome measures, secondary outcome measures, results as they relate to a prior hypothesis); Strengths and limitations of the study (study question, study design, data collection, analysis and interpretation); Interpretation and implications in the context of the totality of evidence (is there a systematic review to refer to, if not, could one be reasonably done here and now?, What this study adds to the available evidence, effects on patient care and health policy, possible mechanisms)? Controversies raised by this study; and Future research directions (for this particular research collaboration, underlying mechanisms, clinical research). Do not repeat in detail data or other material given in the Introduction or the Results section.

References

List references in alphabetical order. Each listed reference should be cited in text (not in alphabetic order), and each text citation should be listed in the References section. Identify references in text, tables, and legends by Arabic numerals in square bracket (e.g. [10]). Please refer to ICMJE Guidelines (http://www.nlm.nih.gov/bsd/uniform_ requirements.html) for more examples.

Standard journal article

[1] Flink H, Tegelberg Å, Thörn M, Lagerlöf F. Effect of oral iron supplementation on unstimulated salivary flow rate: A randomized, double-blind, placebo-controlled trial. J Oral Pathol Med 2006; 35: 540–7.

[2] Twetman S, Axelsson S, Dahlgren H, Holm AK, Källestål C, Lagerlöf F, *et al*. Caries-preventive effect of fluoride toothpaste: A systematic review. Acta Odontol Scand 2003; 61: 347–55.

Article in supplement or special issue

[3] Fleischer W, Reimer K. Povidone-iodine antisepsis. State of the art. Dermatology 1997; 195 Suppl 2: 3–9.

Corporate (collective) author

[4] American Academy of Periodontology. Sonic and ultrasonic scalers in periodontics. J Periodontol 2000; 71: 1792–801.

Unpublished article

[5] Garoushi S, Lassila LV, Tezvergil A, Vallittu PK. Static and fatigue compression test for particulate filler composite resin with fiber-reinforced composite substructure. Dent Mater 2006.

Personal author(s)

[6] Hosmer D, Lemeshow S. Applied logistic regression, 2nd edn. New York: Wiley-Interscience; 2000.

Chapter in book

[7] Nauntofte B, Tenovuo J, Lagerlöf F. Secretion and composition of saliva. In: Fejerskov O,

Kidd EAM, editors. Dental caries: The disease and its clinical management. Oxford: Blackwell Munksgaard; 2003. pp 7–27.

No author given

[8] World Health Organization. Oral health surveys - basic methods, 4th edn. Geneva: World Health Organization; 1997.

Reference from electronic media

[9] National Statistics Online—Trends in suicide by method in England and Wales, 1979–2001. www.statistics.gov.uk/downloads/theme_health/HSQ 20.pdf (accessed Jan 24, 2005): 7–18. Only verified references against the original documents should be cited. Authors are responsible for the accuracy and completeness of their references and for correct text citation. The number of reference should be kept limited to 20 in case of major communications and 10 for short communications.

More information about other reference types is available at www.nlm.nih.gov/bsd/uniform_ requirements.html, but observes some minor deviations (no full stop after journal title, no issue or date after volume, etc.).

Tables

Tables should be self-explanatory and should not duplicate textual material.

Tables with more than 10 columns and 25 rows are not acceptable.

Table numbers should be in Arabic numerals, consecutively in the order of their first citation in the text and supply a brief title for each.

Explain in footnotes all non-standard abbreviations that are used in each table.

For footnotes use the following symbols, in this sequence: *, ¶, †, ‡‡,

Illustrations (Fig.s)

Graphics files are welcome if supplied as Tiff, EPS, or PowerPoint files of minimum 1200x1600 pixel size. The minimum line weight for line art is 0.5 point for optimal printing.

When possible, please place symbol legends below the Fig. instead of the side.

Original color Fig.s can be printed in color at the editor's and publisher's discretion provided the author agrees to pay.

Type or print out legends (maximum 40 words, excluding the credit line) for illustrations using double spacing, with Arabic numerals corresponding to the illustrations.

Sending a revised manuscript

While submitting a revised manuscript, contributors are requested to include, along with single copy of the final revised manuscript, a photocopy of the revised manuscript with the changes underlined in red and copy of the comments with the point-to-point clarification to each comment. The manuscript number should be written on each of these documents. If the manuscript is submitted online, the contributors' form and copyright transfer form has to be submitted in original with the signatures of all the contributors within two weeks of submission. Hard copies of images should be sent to the office of the journal. There is no need to send printed manuscript for articles submitted online.

Reprints

Journal provides no free printed, reprints, however a author copy is sent to the main author and additional copies are available on payment (ask to the journal office).

Copyrights

The whole of the literary matter in the journal is copyright and cannot be reproduced without the written permission.

Declaration

A declaration should be submitted stating that the manuscript represents valid work and that neither this manuscript nor one with substantially similar content under the present authorship has been published or is being considered for publication elsewhere and the authorship of this article will not be contested by any one whose name(s) is/are not listed here, and that the order of authorship as placed in the manuscript is final and accepted by the co-authors. Declarations should be signed by all the authors in the order in which they are mentioned in the original manuscript. Matters appearing in the Journal are covered by copyright but no objection will be made to their reproduction provided permission is obtained from the Editor prior to publication and due acknowledgment of the source is made.

Approval of Ethics Committee

We need the Ethics committee approval letter from an Institutional ethical committee (IEC) or an institutional review board (IRB) to publish your Research article or author should submit a statement that the study does not require ethics approval along with evidence. The evidence could either be consent from patients is available and there are no ethics issues in the paper or a letter from an IRB stating that the study in question does not require ethics approval.

Abbreviations

Standard abbreviations should be used and be spelt out when first used in the text. Abbreviations should not be used in the title or abstract.

Checklist

- Manuscript Title
- Covering letter: Signed by all contributors
- Previous publication/ presentations mentioned, Source of funding mentioned
- Conflicts of interest disclosed

Authors

- Middle name initials provided.
- Author for correspondence, with e-mail address provided.
- Number of contributors restricted as per the instructions.
- Identity not revealed in paper except title page (e.g. name of the institute in Methods, citing previous study as 'our study')

Presentation and Format

- Double spacing
- Margins 2.5 cm from all four sides
- Title page contains all the desired information. Running title provided (not more than 50 characters)
- Abstract page contains the full title of the manuscript
- Abstract provided: Structured abstract provided for an original article.
- Keywords provided (three or more)
- Introduction of 75-100 words
- Headings in title case (not ALL CAPITALS). References cited in square brackets
- References according to the journal's instructions

Language and grammar

- Uniformly American English
- Abbreviations spelt out in full for the first time. Numerals from 1 to l0 spelt out
- Numerals at the beginning of the sentence spelt out

Tables and Fig.s

- No repetition of data in tables and graphs and in text.
- Actual numbers from which graphs drawn, provided.
- Fig.s necessary and of good quality (color)
- Table and Fig. numbers in Arabic letters (not Roman).
- Labels pasted on back of the photographs (no names written)
- Fig. legends provided (not more than 40 words)
- Patients' privacy maintained, (if not permission taken)
- Credit note for borrowed Fig.s/tables provided
- Manuscript provided on a CDROM (with double spacing)

Submitting the Manuscript

- Is the journal editor's contact information current?
- Is the cover letter included with the manuscript? Does the letter:

1. Include the author's postal address, e-mail address, telephone number, and fax number for future correspondence?
2. State that the manuscript is original, not previously published, and not under concurrent consideration elsewhere?
3. Inform the journal editor of the existence of any similar published manuscripts written by the author?
4. Mention any supplemental material you are submitting for the online version of your article. Contributors' Form (to be modified as applicable and one signed copy attached with the manuscript)

SUBSCRIPTION FORM

I want to renew/subscribe international class journal "**Indian Journal of Obstetrics and Gynecology**" of Red Flower Publication Pvt. Ltd.

Subscription Rates:
- Institutional: INR 10500/USD 820.31

Name and complete address (in capitals):_____

_____

Payment detail:
Online payment link: http://rfppl.co.in/payment.php?mid=15

Cheque/DD: Please send the US dollar check from outside India and INR check from India made payable to 'Red Flower Publication Private Limited'. Drawn on Delhi branch.

Wire transfer/NEFT/RTGS:
Complete Bank Account No. 604320110000467
Beneficiary Name: Red Flower Publication Pvt. Ltd.
Bank & Branch Name: Bank of India; Mayur Vihar
MICR Code: 110013045
Branch Code: 6043
IFSC Code: BKID0006043 (used for RTGS and NEFT transactions)
Swift Code: BKIDINBBDOS

Term and condition for supply of journals
1. Advance payment required by Demand Draft payable to **Red Flower Publication Pvt. Ltd**. payable at **Delhi.**
2. Cancellation not allowed except for duplicate payment.
3. Agents allowed 12.5% discount.
4. Claim must be made within six months from issue date.

Mail all orders to
Subscription and Marketing Manager
Red Flower Publication Pvt. Ltd.
48/41-42, DSIDC, Pocket-II
Mayur Vihar Phase-I
Delhi - 110 091(India)
Phone: 91-11-79695648
Cell: +91-9821671871
E-mail: sales@rfppl.co.in