Online ISSN : 2249-4618
Print ISSN : 0975-5888
DOI : 10.17406/GJMRA

Global Journal

of Medical Research: E

Gynecology & Obstetrics

Highlights

The Role of Progesterone

Prediction of Preterm Delivery

Premature Rupture of Membranes

Prevalence and Determinants of Stillbirth

Discovering Thoughts, Inventing Future

VOLUME 23 ISSUE 1 VERSION 1.0

Global Journal of Medical Research: E
Gynecology and Obstetrics

Global Journal of Medical Research: E
Gynecology and Obstetrics

Volume 23 Issue 1 (Ver. 1.0)

Open Association of Research Society

This is a special issue published in version 1.0 of "Global Journal of Medical Research." By Global Journals Inc.

Incorporation No.: 0423089
License No.: 42125/022010/1186
Registration No.: 430374
Import-Export Code: 1109007027
Employer Identification Number (EIN):
USA Tax ID: 98-0673427

Global Journals Inc.

*(A Delaware USA Incorporation with "Good Standing"; **Reg. Number: 0423089**)*

Sponsors: Open Association of Research Society
Open Scientific Standards

Publisher's Headquarters office

Global Journals® Headquarters
945th Concord Streets,
Framingham Massachusetts Pin: 01701,
United States of America
USA Toll Free: +001-888-839-7392
USA Toll Free Fax: +001-888-839-7392

Offset Typesetting

Global Journals Incorporated
2nd, Lansdowne, Lansdowne Rd., Croydon-Surrey,
Pin: CR9 2ER, United Kingdom

Packaging & Continental Dispatching

Global Journals Pvt Ltd
E-3130 Sudama Nagar, Near Gopur Square,
Indore, M.P., Pin:452009, India

Find a correspondence nodal officer near you

To find nodal officer of your country, please email us at *local@globaljournals.org*

eContacts

Press Inquiries: *press@globaljournals.org*
Investor Inquiries: *investors@globaljournals.org*
Technical Support: *technology@globaljournals.org*
Media & Releases: *media@globaljournals.org*

Pricing (Excluding Air Parcel Charges):

Yearly Subscription (Personal & Institutional)
250 USD (B/W) & 350 USD (Color)

Editorial Board

Global Journal of Medical Research

Dr. Han-Xiang Deng

MD., Ph.D
Associate Professor and Research Department
Division of Neuromuscular Medicine
Davee Department of Neurology and Clinical Neurosciences
Northwestern University Feinberg School of Medicine
Web: neurology.northwestern.edu/faculty/deng.html

Dr. Pina C. Sanelli

Associate Professor of Radiology
Associate Professor of Public Health
Weill Cornell Medical College
Associate Attending Radiologist
NewYork-Presbyterian Hospital
MRI, MRA, CT, and CTA
Neuroradiology and Diagnostic Radiology
M.D., State University of New York at Buffalo,
School of Medicine and Biomedical Sciences
Web: weillcornell.org/pinasanelli/

Dr. Roberto Sanchez

Associate Professor
Department of Structural and Chemical Biology
Mount Sinai School of Medicine
Ph.D., The Rockefeller University
Web: mountsinai.org/

Dr. Michael R. Rudnick

M.D., FACP
Associate Professor of Medicine
Chief, Renal Electrolyte and Hypertension Division (PMC)
Penn Medicine, University of Pennsylvania
Presbyterian Medical Center, Philadelphia
Nephrology and Internal Medicine
Certified by the American Board of Internal Medicine
Web: uphs.upenn.edu/

Dr. Feng Feng

Boston University
Microbiology
72 East Concord Street R702
Duke University
United States of America

Dr. Seung-Yup Ku

M.D., Ph.D., Seoul National University Medical College,
Seoul, Korea Department of Obstetrics and Gynecology
Seoul National University Hospital, Seoul, Korea

Dr. Hrushikesh Aphale

MDS- Orthodontics and Dentofacial Orthopedics.
Fellow- World Federation of Orthodontist, USA.

Santhosh Kumar

Reader, Department of Periodontology,
Manipal University, Manipal

Gaurav Singhal

Master of Tropical Veterinary Sciences, currently pursuing Ph.D in Medicine

Dr. Aarti Garg

Bachelor of Dental Surgery (B.D.S.) M.D.S. in Pedodontics and Preventive Dentistr Pursuing Phd in Dentistry

Sabreena Safuan

Ph.D (Pathology) MSc (Molecular Pathology and Toxicology) BSc (Biomedicine)

Getahun Asebe

Veterinary medicine, Infectious diseases, Veterinary Public health, Animal Science

Dr. Suraj Agarwal

Bachelor of dental Surgery Master of dental Surgery in Oromaxillofacial Radiology.
Diploma in Forensic Science & Oodntology

Osama Alali

PhD in Orthodontics, Department of Orthodontics, School of Dentistry, University of Damascus. Damascus, Syria. 2013 Masters Degree in Orthodontics.

Prabudh Goel

MCh (Pediatric Surgery, Gold Medalist), FISPU, FICS-IS

Raouf Hajji

MD, Specialty Assistant Professor in Internal Medicine

Surekha Damineni

Ph.D with Post Doctoral in Cancer Genetics

Arundhati Biswas

MBBS, MS (General Surgery), FCPS, MCh, DNB (Neurosurgery)

Rui Pedro Pereira de Almeida

Ph.D Student in Health Sciences program, MSc in Quality Management in Healthcare Facilities

Dr. Sunanda Sharma

B.V.Sc.& AH, M.V.Sc (Animal Reproduction, Obstetrics & gynaecology), Ph.D.(Animal Reproduction, Obstetrics & gynaecology)

Shahanawaz SD

Master of Physiotherapy in Neurology PhD- Pursuing in Neuro Physiotherapy Master of Physiotherapy in Hospital Management

Dr. Shabana Naz Shah

PhD. in Pharmaceutical Chemistry

Vaishnavi V.K Vedam

Master of dental surgery oral pathology

Tariq Aziz

PhD Biotechnology in Progress

Contents of the Issue

Global Journal of Medical Research: E
Gynecology and Obstetrics
Volume 23 Issue 1 Version 1.0 Year 2023
Type: Double Blind Peer Reviewed International Research Journal
Publisher: Global Journals
Online ISSN: 2249-4618 & Print ISSN: 0975-5888

Parturition is not the Mirror Image of Implantation: The Role of Progesterone

By Hisham Arab

Abstract- There has been an abundance of evidence from clinical, animal, and in vitro studies that progesterone (P4) is important for establishing, maintaining, and terminating a pregnancy. P4 exerts its primary action via its two receptors: progesterone receptor A (PGR-A) and B (PGR-B). Analyses of transcriptome and cistrome genome have unearthed novel members and modifiers of the P4 signaling pathway. The increase in serum P4 levels and down-regulation of PGR-B are important in the development of pinopodes, thus marking implantation. Additionally, it promotes the quiescent myometrial cell phenotype, and the inhibition of its production in myometrial cells induces labor and is the key physiologic initiator of parturition. Through genomic and non-genomic intracellular mechanisms involving these PGR isoforms, various physiologic states can be determined such as the quiescent and contractile myometrium during pregnancy.

Keywords: progesterone, implantation, parturition, progesterone receptor, PGR gene, genetic pathways.

GJMR-E Classification: DDC Code: 618.2 LCC Code: RG525

Strictly as per the compliance and regulations of:

Parturition is not the Mirror Image of Implantation: The Role of Progesterone

Hisham Arab

Abstract- There has been an abundance of evidence from clinical, animal, and in vitro studies that progesterone (P4) is important for establishing, maintaining, and terminating a pregnancy. P4 exerts its primary action via its two receptors: progesterone receptor A (PGR-A) and B (PGR-B). Analyses of transcriptome and cistrome genome have unearthed novel members and modifiers of the P4 signaling pathway. The increase in serum P4 levels and down-regulation of PGR-B are important in the development of pinopodes, thus marking implantation. Additionally, it promotes the quiescent myometrial cell phenotype, and the inhibition of its production in myometrial cells induces labor and is the key physiologic initiator of parturition. Through genomic and non-genomic intracellular mechanisms involving these PGR isoforms, various physiologic states can be determined such as the quiescent and contractile myometrium during pregnancy. It has been found that PGR's ability to transduce P4 signaling can be modulated by several layers of control, including transcriptional regulation of the PGR gene, post-translational modification of the PGR protein, stoichiochemistry of PGR isoforms, and interaction of PGR and co-regulators on downstream targets. This review aims to describe the genetic role of P4 and specifically its receptor in implantation and parturition, and how it affects the evolution of pregnancy.

Keywords: progesterone, implantation, parturition, progesterone receptor, PGR gene, genetic pathways.

Abbreviations

P4: progesterone
PGR: progesterone receptor
PGR-A: progesterone receptor-A
PGR-B: progesterone receptor-B
RNA: ribonucleic acid
Ihh: Indian hedgehog
COUP-TFII: effector chicken ovalbumin upstream promoter transcription factor II
HAND2: heart and neural crest derivatives expressed transcript 2
FGF-ERK: fibroblast growth factor-extracellular signal-regulated kinase
EGFR: epidermal growth factor receptor
WNT4: wingless-type MMTV integration site family member 4
BMP2: bone morphogenetic protein 2
WNK1: serine/threonine protein kinase: With-No-Lysine (K) 1
MAPK-7: mitogen-activated protein kinase -7
DNA: deoxyribonucleic acid
NF-$_{k}$B: nuclear factor kappa-light-chain-enhancer of activated B cells
AP-1: activator protein-1
I$_{K}$B$_{\alpha}$: nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha
MAPK: mitogen-activated kinase
MKP-1: mitogen-activated kinase phosphatase-1
ZEB1: Zinc finger E-box-binding homeobox 1
CX43: connexin 43or GJA1: gap junction alpha 1
OXTR: oxytocin receptor
COX-2: cyclooxygenase-2
PgF2αR: prostanoid FP receptor
miR-200: microRNA-200
ZEB2: zinc finger E-box-binding homeobox 2
STAT5b: signal transducer and activator of transcription 5b
20α-HSD: 20α-hydroxysteroid dehydrogenase
AP-1: activator protein 1
FOS: transcription factor FBJ osteosarcoma oncogene
JUN: jun proto-oncogene
FOSL2: fos-like antigen 2
CAPs: contraction-associated proteins
F2a: prostaglandin receptor
IL-1: interleukin-1
IL-6: interleukin-6
IL-8: interleukin-8

I. Introduction

The pregnant state has baffled scientists since the beginning of time. The process of implantation, all the way through parturition has been the subject of extensive studies, as complex pathways at the neuroendocrine and immunological levels interact to establish and sustain a complex fetus. Alongside the hormonal changes that typically occur upon implantation and parturition, gene expression profiling studies have attempted to identify the signals that trigger these occurrences to provide insight into causative pathophysiological conditions and suggest treatment modalities to aid conception and prevent preterm births.

The common denominator between the above two states of pregnancy appears to be progesterone (P4). P4, an essential hormone in the regulation of

Author: MD, FRCSC, FACOG, Program Director at Maternal & Fetal Health Program, Dr. Arab Medical Center, Building 3848, Alhayat Plaza, Prince Saud Alfaisal Street, Jeddah Saudi Arabia.
e-mail: arab123@gmail.com

female reproduction, acts primarily in the uterus: in particular, through preparing the endometrium for implantation after the ovulation and fertilization of an oocyte, and the maintenance of an ensuing pregnancy by promoting uterine growth and suppressing myometrial contractility [1, 2]. The ovary is the major site of synthesis and secretion of progesterone in the mammal, which in turn induces cyclical fluctuations in the levels of P4 in circulation [1].

The effects of P4 are facilitated by the nuclear progesterone receptor (PGR), which operates through nuclear transcription regulators that are ligand-activated [1, 2]. They are similar to other receptors for steroids, thyroid hormones, retinoids, and vitamin D3. The human PGR, a member of the NR3C3 subfamily of the nuclear receptor super family, is comprised of two isoforms: the full-length PGR-B and the truncated (by 164 N terminal amino acids) PGR-A [3]. The two receptor proteins are encoded by a single gene [located on human chromosome 11 (11q22-q23)] under the control of different promoters, each of which gives rise to a diverse subgroup of PGR messenger ribonucleic acid (mRNA) species [4].

The function of both receptors, similar to other steroid hormone receptors, is mainly via ligand-activated transcription factors. It appears that when the PGR-A level exceeds that of PGR-B, the latter will get suppressed. It is well known that PGR-B dominates throughout pregnancy and that P4 promotes myometrial relaxation via PGR-B-mediated genomic actions in myometrial cells to ensure myometrial quiescence. However, this is inhibited near term and during labor as myometrial cell expression of PGR-A increases leading to a PGR-A: PGR-B ratio of 3 or more. This leads to the conclusion that PGR-A is an endogenous repressor of PGR-B, and that genomic P4 responsiveness is inversely related to the PGR-A: PGR-B ratio [1, 3]. This differential expression of the progesterone receptor isoforms, PGR-A and PGR-B, contributes to a functional withdrawal of P4 and the onset of labor.

Furthermore, the role of a repressor that PGR-A plays appears to extend beyond its actions on PGR-B. It has been shown that PGR-A reduces the response of additional hormone receptors such as androgen, mineralocorticoid, glucocorticoid, and estrogen receptors to their appropriate ligands [5]. In the human myometrium, transcriptomic data reaffirmed that overexpression of PGR-B resulted in relaxed myometrium not responding to oxytocin stimulation, while the overexpression of myometrial PGR-A demonstrated a twofold increase in contractility in response to uterotonic agents [6].

The expression of PGR has also been described in other tissues which have been known to be responsive to P4, for example, the uterus, the ovary, and preovulatory granulosa cells [1]. Moreover, the expression of the P4 receptors, and therefore its sensitivity to progestins, seems to be controlled by estrogen, which increases the expression of PGR in most target tissues as opposed to P4, which decreases its expression [1].

Recent advances in the understanding of the process of parturition in humans have revealed a monumental finding. In 2003, Girotti and Zingg reported that concerning the expression of certain genes, the parturition phase represents a mirror image of the implantation phase [7]. In this narrative review, we hypothesize that the quiescent phase of pregnancy is a mirror image of parturition, whereas the implantation phase is not quite the opposite of it. While the common denominator between all phases is P4 and its receptor, there are many known and unknown mechanisms and pathways that operate differently in these phases.

II. Role of Progesterone and its Receptor in Implantation

A fruitful implantation of the embryo in the uterus necessitates an apt embryo, an amenable uterus, and complex harmonization between the two. For most mammals, the receptiveness of the uterus is time-sensitive; a window of receptivity lasting around 24 hours in mice and 2 to 3 days in humans is tightly controlled by two ovarian hormones: estrogen and progesterone [8].

Preparing the uterus for implantation is initiated by an epithelium-stroma crosstalk that has been proven to be regulated by PGR in several studies [9, 10]. The PGR in the endometrial epithelium mediates the signal from P4 to transcriptionally amplify the levels of Indian hedgehog (Ihh) signaling proteins before the embryo has been implanted. This increased epithelial Ihh then initiates the stromal hedgehog pathway to stimulate the expression of the downstream effector chicken ovalbumin upstream promoter transcription factor II (COUP-TFII). On the stromal cell side, COUP-TFII decreases estrogen signaling and stops epithelial proliferation, most likely via the heart and neural crest derivatives expressed transcript 2 (HAND2) orchestrated reduction of the fibroblast growth factor-extracellular signal-regulated kinase (FGF-ERK) pathway. However, it is unclear whether COUP-TFII mediates HAND2 directly or through PGR in the stroma, though COUP-TFII does directly promote PGR expression in the stroma and P4 does increase stromal HAND2 levels. At the physiological level, this initiation of crosstalk by epithelial PGR leads to a shift in the state of epithelial cells; from being proliferative into a state of differentiation, and hence ready for ensuing embryo implantation [8].

Additionally, the above epithelial pathway prepares the stroma for decidualization via COUP-TFII and in combination with epidermal growth factor receptor (EGFR) signaling in the stroma. Studies have found that in mouse models and cultured human

endometrial cells, stromal COUP-TFII stimulates the expression of wingless-type MMTV integration site(WNT) family member 4 (WNT4) and thus stimulates decidualization. Furthermore, studies in mice with a uterus that is deficient in COUP-TFII have reported results of a positive regulatory function for COUP-TFII on the expression of bone morphogenetic protein 2 (BMP2) [11]. Downstream of BMP2, WNT4 is positively regulated by PGR and a member of the O-class of forkhead box (FOX) proteins, FOXO1 *(Figure 1)*. It appears that stromal EGFR signals converge with the PR-IHH axis at BMP2 and WNT4 to affect decidualization [12]. Further downstream, researchers have speculated that the familiar serine/threonine proteinkinase: With-No-Lysine (K) 1 (WNK1) – mitogen-activated protein kinase -7 (MAPK-7) axis may act subsequently of the EGFR pathway for decidualization in the stroma; however this role is still unclear[13]. Both PGR isoforms are important for pregnancy success in humans, with the PGR-B isoform playing a predominant role in decidualization [14]. Moreover, the endometrial epithelial PGR expression markedly decreases in the mid-secretory phase to enable normal uterine receptivity to occur. At the same time, it continues its abundance in stromal cells to maintain decidualization. Epithelial FOXO1 expression, on the other hand, is extremely high at this stage. This reciprocal expression relationship between PGR and FOXO1 is considered a critical step in the establishment of endometrial receptivity [2].

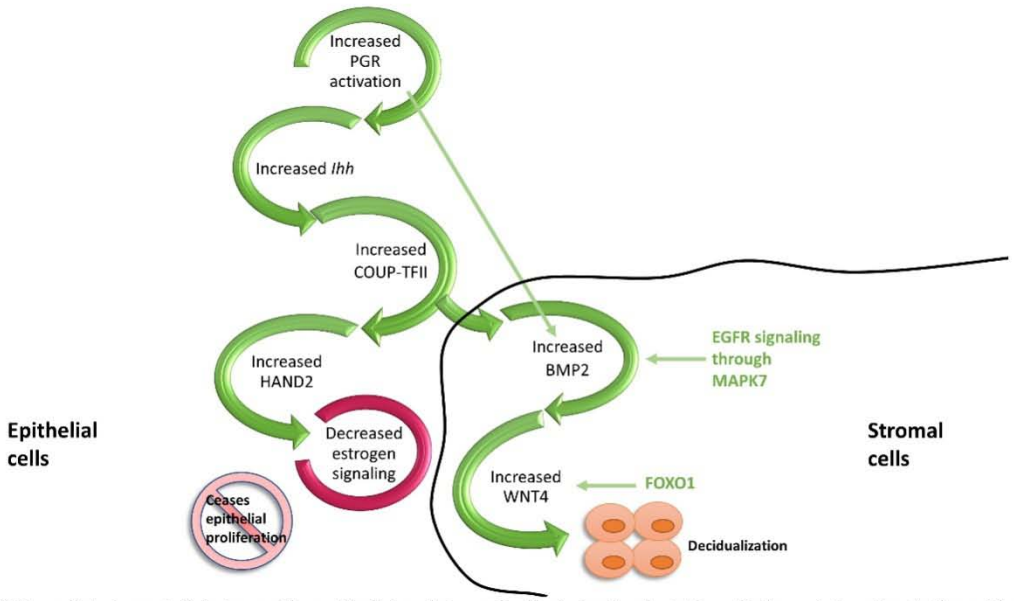


Figure 1. PGR-mediated crosstalk between the epithelial and stromal cells during implantation. P4 through its action in the epithelial cells initiates the *Ihh* axis which, in turn signals COUP-TFII and HAND2 to decrease estrogen-dependent proliferation. While at the stromal level, increased FOXO1 and hence increased WNT4 and BMP2 leads to decidualization.

Studies assessing the multiple processes involved in implantation and promoting receptivity of the uterus have recently highlighted the role of the pinopode in favorable fertility outcomes. The pinopode or the uterodome consists of small microvilli protrusions, flowerlike shapes, which develop on the apical surface of the luminal epithelium of the endometrium that is hormonally regulated [15]. Uterodomes are characterized by the presence of cell-adhesion molecules (integrins). P4 is responsible for the timely downregulation of estrogen receptors, an effect linked to the timely expression of integrin αvβ3, which plays a role in blastocyst adhesion to the uterus. This is why several studies have stressed the dependency of pinopode formation on the two most studied hormones contributing to fertility, estrogen, and progesterone [16, 17]. The αvβ3 integrin is regulated by a homeobox protein, the HOXA10 transcription factor, whose regulation is also controlled by P4.

The science so far has shown that other hormones such as adrenomedullin lead to an increase in pinopode growth; testosterone however leads to their decrease [18, 19]. It is therefore important to understand how hormones regulate pinopode growth and further investigate these relations.

III. Role of Progesterone and its Receptor in Quiescence

Human uterine quiescence is characterized by an anti-inflammatory atmosphere generated through the myometrial PGR-B, the dominant isoform during this stage. It maintains the quiescent state throughout gestation by suppressing the transcription of genes encoding contraction-associated proteins (CAPs) [such as connexin43 (GJA1/CX43), prostaglandin receptor (F2a), and oxytocin receptor (OXTR)]; and by suppressing inflammatory genes, like nuclear factor kappa-light-chain-enhancer of activated B cells (NF-$_k$B)

and interleukin-1(IL-1). Maintaining the quiescent state during pregnancy requires multifaceted and complex mechanisms that involve P4-PGR mediated interactions through genomic and non-genomic pathways.

Simply these pathways will lead to first of all theinhibition of the well-known contractile genes like CX43 and OXTR, by upregulating the expression of the transcriptional inhibitor zinc finger E-box-binding homeobox 1 (ZEB1) that binds to their promoters and suppress their expression to ensure the quiescent stage of pregnancy [20]. Additionally, these pathways will lead to the antagonizing of the proinflammatory transcription factors by direct interaction of PGR with NF-$_k$B or activator protein-1 (AP-1). Evidence exists to support the notion that progesterone may directly or indirectly impair the NF-$_k$B-mediated inflammatory cascade leading to labor. Experimental work has demonstrated that a mutual negative interaction exists between the PGR and NF-$_k$B p65. Moreover, in human lower uterine segment fibroblasts and amnion epithelial cells, P4 was found to repress NF-$_k$B transcriptional activity [21]. On the other hand, the repressor effect of PGR coupling with jun proto-oncogene (JUN)protein, a subfamily of the AP-1, to maintain myometrial quiescence has been suggested strongly by researchers [22]. Activated AP-1 is known to increase multiple pro-inflammatory cytokines [IL-1, interleukin-6 (IL-6), and interleukin-8(IL-8)] in the laboring human myometrium[23].

Furthermore, these pathways will influence the expression of genes that block proinflammatory transcription factors such as the NF-$_k$B inhibitor, nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha (I_kB_α) - which prevents activation and nuclear translocation of NF-$_k$B p50 and p65 - and the mitogen-activated kinase (MAPK) inhibitor, MAPK phosphatase-1 (MKP-1 or DUSP1); which inhibits p38 MAPK activation and NF-$_k$B p65 nuclear translocation. As a result, P4-activated PGR maintains the quiescent state by inhibiting the activation of inflammatory response pathways[20].

The progesterone block hypothesis, first proposed by George Corner in 1942 and later expanded by Arpad Csapo in the 1950s, posits that P4 maintains pregnancy by blocking labor and that withdrawal of the P4 block is a key trigger for parturition[3].

IV. Role of Progesterone and its Receptor in Parturition

Parturition is the result of complex maternal and fetal interactions, whereby the quiescent uterus builds synchronized contractions and the cervix dilates to allow passage of the fetus through the birth canal [24]. For a successful result, maturation of fetal organs is required to ensure survival outside the uterus, in addition to maternal changes necessary to initiate lactation postpartum. As such, synchronized stimuli from both the mature fetus and the active uterus is desirable, with most evidence suggesting that the fetus itself triggers these two events [24].

Inhibition of P4 production or its function elicits labor by inducing inflammation of the decidua, remodeling of the cervix, promoting rupture of the fetal membrane, and increasing myometrial contractility [25]. The “progesterone receptor isoform switch” concept was posited to explain the transition from a quiescent to a contractile myometrial phenotype in the presence of high levels of progesterone [6]. At parturition, the rise in PGR-A expression promotes labor by inhibiting the anti-inflammatory actions of PGR-B and stimulating proinflammatory gene expression in response to progesterone [3].

The interplay of several genes, receptors, and enzymes affects the process of contractions in the myometrium. Studies so far have agreed on 5 genes and maybe more, that regulate the shift from the quiescent state to parturition. These genes - cyclooxygenase-2 (COX-2); prostanoid FP receptor (PgF2αR); OXTR; CX43; and gap junction protein – either suppress or activate muscular contractions thus leading to labor.

The increase in local metabolism of P4 in the myometrium and decrease in PGR function in the uterus and cervix near term is critical for parturition to commence in all mammals. Findings by Renthal et al (2015) revealed that the pivotal role that ZEB1 serves in myometrial contractility during pregnancy and labor is through mediating the opposite actions of P4 and estrogen. During the quiescent state, the elevated levels of P4 and the increased function of its receptors promote the upregulation of myometrial ZEB1. This increase leads to the inhibition of expression of the microRNA-200 (miR-200) family and the suppression of both OXTR and CX43. The decreased levels of miR-200 up-regulates ZEB1 further and increase zinc finger E-box-binding homeobox 2 (ZEB2), thus binding response elements upstream of the miR-199a/214 clusters to enhance its expression, which eventually suppresses COX-2, and block the contractile prostaglandins biosynthesis. The low levels of miR-200s allow the up-regulation of the transcription factor, signal transducer, and activator of transcription 5B (STAT5b), which inhibits expression of 20α-hydroxysteroid dehydrogenase (20α-HSD), and as such permits local myometrium levels of P4 to remain elevated [20].

As pregnancy transitions to labor, the decreased function of P4/PGR in the myometrium and increased circulating levels of estrogen and the activity of its receptor cause the downregulation of ZEB1. This then induces the miR-200 family and hence causes further suppression of ZEB1 and ZEB2, which in turn allows the up-regulation of expression of OXTR and CX43. The decreased levels of ZEB1/2 also lead to a decrease in expression of the miR199a/214 cluster,

which allows the up-regulation of COX-2 and increased synthesis of contractile prostaglandins. The high expression of miR-200 inhibits STAT5b and as such permits the increased transcription of 20α-HSD, which metabolizes P4 into inactive products in the myometrium [20]. Collectively, these molecular events contribute to the induction of contractions in the uterus and therefore lead to labor *(Figure 2)*.

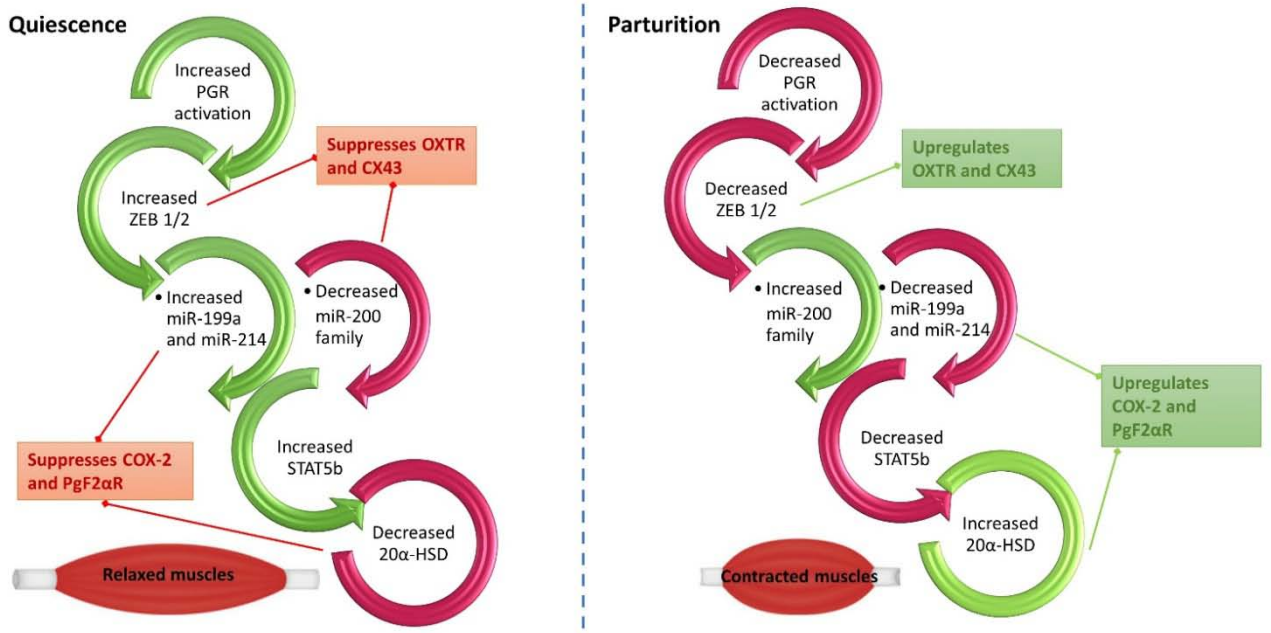


Figure 2. P4 and PGR mediation of quiescence and parturition. The regulation of PGR impacts ZEB1/2 and hence quiescence during pregnancy or contractility during labor.

Myometrial muscle cells contract together to generate a synchronized movement through the presence of intercellular bridges or gap junctions [26]. One protein that has been described when mediating the formation of gap junctions as term approaches is Gap junction alpha 1 (GJA1), also known as CX43.The reporter expression downstream of a synthetic GJA1 promoter is increased by co-expression of constructs encoding members of the AP-1 transcription factor; namely FBJ osteosarcoma oncogene (FOS) and JUN subfamilies. In humans, it appears that the levels of JUN protein remain relatively constant in the myometrium throughout gestation, whereas an increase in levels of FOS and Fos-like antigen 2 (FOSL2) proteins is reported during labor inside the nuclei of the myometrial cells. Several JUN subfamily members are present in the uterine smooth muscle during the quiescent phase of pregnancy. It is therefore possible that the JUN family plays a role in maintaining the quiescence, and that they require heterodimerization with a partner from the FOS subfamily to stimulate genes for the initiation of labor [26].

V. Conclusion

While inflammatory changes are required for both implantation and parturition, the genetic process is totally different between the two phases. The studies conducted so far have not identified similar pathways when it comes to genetic mediation of implantation and labor. It appears that the only common denominator between these two phases of pregnancy is P4 and its receptors, PGR-A and PGR-B. Further research is needed to determine whether these two phases are indeed mirrored images as the data so far indicates that quiescence and parturition are the true mirror images.

References Références Referencias

1. Graham, J.D. and C.L. Clarke, Physiological Action of Progesterone in Target Tissues*. Endocrine Reviews, 1997. 18(4): p. 502-519.
2. DeMayo, F.J., and J.P. Lydon, 90 YEARS OF PROGESTERONE: New insights into progesterone receptor signaling in the endometrium required for embryo implantation. Journal of molecular endocrinology, 2020. 65(1): p. T1-T14.
3. Tan, H., et al., Progesterone receptor-A and -B have opposite effects on proinflammatory gene expression in human myometrial cells: implications for progesterone actions in human pregnancy and parturition. J Clin Endocrinol Metab, 2012. 97(5): p. E719-30.
4. Kastner, P., et al., Two distinct estrogen-regulated promoters generate transcripts encoding the two functionally different human progesterone receptor forms A and B. Embo j, 1990. 9(5): p. 1603-14.

5. Wen, D.X., et al., The A and B isoforms of the human progesterone receptor operate through distinct signaling pathways within target cells. Mol Cell Biol, 1994. 14(12): p. 8356-64.
6. Peavey, M.C. and S.P. Wu, Progesterone receptor isoform B regulate the Oxtr-Plcl2-Trpc3 pathway to suppress uterine contractility. 2021. 118(11).
7. Girotti, M. and H.H. Zingg, Gene Expression Profiling of Rat Uterus at Different Stages of Parturition. Endocrinology, 2003. 144(6): p. 2254-2265.
8. Wu, S.P., R. Li, and F.J. DeMayo, Progesterone Receptor Regulation of Uterine Adaptation for Pregnancy. Trends Endocrinol Metab, 2018. 29(7): p. 481-491.
9. Tan, J., et al., Differential uterine expression of estrogen and progesterone receptors correlates with uterine preparation for implantation and decidualization in the mouse. Endocrinology, 1999. 140(11): p. 5310-21.
10. Wetendorf, M., et al., Decreased epithelial progesterone receptor A at the window of receptivity is required for preparation of the endometrium for embryo attachment. Biology of reproduction, 2017. 96(2): p. 313-326.
11. Kurihara, I., et al., COUP-TFII mediates progesterone regulation of uterine implantation by controlling ER activity. PLoS genetics, 2007. 3(6): p. e102.
12. Large, M.J., et al. The epidermal growth factor receptor critically regulates endometrial function during early pregnancy. PLoS genetics, 2014. 10, e1004451 DOI: 10.1371/journal.pgen.1004451.
13. Adams, N.R., et al., WNK lysine deficient protein kinase 1 regulates human endometrial stromal cell decidualization, proliferation, and migration in part through mitogen-activated protein kinase 7. Biology of Reproduction, 2017. 97(3): p. 400-412.
14. Kaya, H.S., et al., Roles of Progesterone Receptor A and B Isoforms during Human Endometrial Decidualization. Molecular Endocrinology, 2015. 29(6): p. 882-895.
15. Quinn, K.E., et al., Pinopodes: Recent advancements, current perspectives, and future directions. Mol Cell Endocrinol, 2020. 501: p. 110644.
16. Lopata, A., U. Bentin-Ley, and A. Enders, "Pinopodes" and implantation. Rev Endocr Metab Disord, 2002. 3(2): p. 77-86.
17. Rarani, F.Z., F. Borhani, and B. Rashidi, Endometrial pinopode biomarkers: Molecules and microRNAs. 2018. 233(12): p. 9145-9158.
18. Matson, B.C., et al., Adrenomedullin improves fertility and promotes pinopodes and cell junctions in the peri-implantation endometrium. Biol Reprod, 2017. 97(3): p. 466-477.
19. Mokhtar, H.M., et al., Testosterone decreases the expression of endometrial pinopode and L-selectin ligand (MECA-79) in adult female rats during the uterine receptivity period. Int J Clin Exp Pathol, 2014. 7(5): p. 1967-76.
20. Renthal, N.E., et al., Molecular Regulation of Parturition: A Myometrial Perspective. Cold Spring Harb Perspect Med, 2015. 5(11).
21. Hardy, D.B., et al., Progesterone Receptor Plays a Major Antiinflammatory Role in Human Myometrial Cells by Antagonism of Nuclear Factor-κB Activation of Cyclooxygenase 2 Expression. Molecular Endocrinology, 2006. 20(11): p. 2724-2733.
22. Nadeem, L., et al., Molecular evidence of functional progesterone withdrawal in human myometrium. Nature Communications, 2016. 7(1): p. 11565.
23. MacIntyre, D.A., et al., Activator protein 1 is a key terminal mediator of inflammation-induced preterm labor in mice. The FASEB Journal, 2014. 28(5): p. 2358-2368.
24. Challis, J.R.G., et al., Endocrine and paracrine regulation of birth at term and preterm. Endocr Rev, 2000. 21(5): p. 514-50.
25. Guzeloglu-Kayisli, O., et al., Decidual cell FKBP51-progesterone receptor binding mediates maternal stress-induced preterm birth. Proceedings of the National Academy of Sciences of the United States of America, 2021. 118(11): p. e2010282118.
26. Shchuka, V.M., et al., The pregnant myometrium is epigenetically activated at contractility-driving gene loci before the onset of labor in mice. PLOS Biology, 2020. 18(7): p. e3000710.

Global Journal of Medical Research: E
Gynecology and Obstetrics
Volume 23 Issue 1 Version 1.0 Year 2023
Type: Double Blind Peer Reviewed International Research Journal
Publisher: Global Journals
Online ISSN: 2249-4618 & Print ISSN: 0975-5888

Prevalence and Determinants of Stillbirth among Women Attended Deliveries in Dekemhare Hospital: Case-Control Study

By Hailemichael Gebremariam, Yosief Yemane, Natnael Gebregziabher, Teklezghi Ainalem, Berhe Tesfai, Okbu Frezgi, Suzana Tesfay, Danait Tekeste & Fitsum Kibreab

Abstract- *Background:* Stillbirth is one of the vital indicators of quality care; it is one of the adverse outcomes of pregnancy and also it is a growing public health issues worldwide. The outcome of delivery in Dekemhare Hospital has not been investigated. The aim of the study was to determine the prevalence and determinants of stillbirth among women attended deliveries in Dekemhare Hospital.

Methods: A facility-based unmatched case–control study was conducted. Cases were deliveries whose birth outcome was stillbirth and controls were deliveries with live birth. A data extraction tool was developed to collect data from a sample of 552 (138cases and 414 controls).

Keywords: *stillbirth, determinants, PROM, case, neural tube defect, prevalence, Eritrea.*

GJMR-E Classification: *DDC Code: 362.19683 LCC Code: RC521*

Strictly as per the compliance and regulations of:

Prevalence and Determinants of Stillbirth among Women Attended Deliveries in Dekemhare Hospital: Case-Control Study

Hailemichael Gebremariam [α], Yosief Yemane [σ], Natnael Gebregziabher [ρ], Teklezghi Ainalem [ω], Berhe Tesfai [¥], Okbu Frezgi [§], Suzana Tesfay [χ], Danait Tekeste [ν] & Fitsum Kibreab [Θ]

Abstract- Background: Stillbirth is one of the vital indicators of quality care; it is one of the adverse outcomes of pregnancy and also it is a growing public health issues worldwide. The outcome of delivery in Dekemhare Hospital has not been investigated. The aim of the study was to determine the prevalence and determinants of stillbirth among women attended deliveries in Dekemhare Hospital.

Methods: A facility-based unmatched case–control study was conducted. Cases were deliveries whose birth outcome was stillbirth and controls were deliveries with live birth. A data extraction tool was developed to collect data from a sample of 552 (138cases and 414 controls). Data were entered in CSPro 7.2 and analyzed using SPSS version 26. Crude and adjusted odds ratio with 95%CI was calculated and p-value was used to declare statistically significant association.

Results: The prevalence of stillbirth during the study period was 2.5%. Breech delivery (AOR: 10.27; 95%CI: 3.87-27.27), presence of congenital abnormality (AOR: 9.36; 95%CI: 2.47-35.45), referred from other health facility (AOR: 4.71; 95%CI: 2.41-9.17), augmentation or induction of labour (AOR: 4.79; 95%CI: 1.33-17.31), presence of cord accident (AOR: 75.40; 95%CI: 6.57-865.75) were found to be determinant of stillbirth. Conversely use of partograph (AOR: 0.38; 95% CI: 0.20-0.74), presence of pregnancy induced hypertension (AOR: 0.03; 95%CI: 0.03-0.36), premature rupture of membrane (AOR: 0.14; 95% CI: 0.03-0.68) and birth weight above 2500gm (AOR: 0.03; 95%CI: 0.01-0.07) were found to be a protective factor for stillbirth.

Conclusion: Based on this study, we highly recommended on the improvement of health care provider's skill to manage babies presenting in breech position, utilization of partograph during labour, strengthening referral system and monitoring and evaluating of referral practice, improving documentation of antenatal care visits in delivery register. And also timely and early identification of mothers who are at risk for neural tube defect and supplementation of folic acid at preconception.

Author α α ρ: MD, Dekemhare Hospital, Debub Zoba, Ministry of Health, Eritrea. e-mail: gm.haile21@gmail.com
Author ω: BSN, Dekemhare Hospital, Debub Zoba, Ministry of Health, Eritrea.
Author ¥ §: MD, Obstetrics and Gynecology, Post-Graduate, Orotta College of Medicine and Health Science, Ministry of Health, Eritrea.
Author χ: Midwife nurse, Dekemhare Hospital, Debub Zoba, Ministry of Health, Eritrea.
Author ν: Statistician, Godayif Community Hospital, Ministry of Health, Eritrea.
Author Θ: Epidemiologist, MOH Health Research and Resource Center Division, Asmara, Eritrea.

Keywords: stillbirth, determinants, PROM, case, neural tube defect, prevalence, Eritrea.

I. Introduction

Stillbirth is defined as a baby born with no signs of life at or after 28 weeks' gestation.[1, 2] It is one of the growing public health issues worldwide. In 2019, around 2 million babies were stillborn, with worldwide prevalence of 13.9 per 1000 total births.[2-4] Women in sub-Saharan Africa and Southern Asia bear the greatest burden of stillbirths in the world, where 42% and 34% of the global stillbirth occurred in sub-Saharan Africa and Southern Asia respectively. [2, 3] Where as women in Europe, Northern America, Australia and New Zealand bear lower burden of still birth in the world, with 2% of global stillborn babies. [2] There is also large differences by national income group, 27 % of the global stillborn in low income groups compare to 2 % of the global stillborn in high income group. Overall, 40 % of stillbirth occurs during labor. [2, 3, 5] This loss could be avoided with improved monitoring and timely access to emergency obstetric care when required. [6]

This loss reaches far beyond the loss of life. Stillbirth has psychological impacts, such as maternal depression, and profound financial consequences for parents. And also it has long-term economic impacts for society. [7] But this traumatic loss of life remains a neglected issue. [2] They are invisible in policies and programs and underfinanced as an area requiring intervention. Targets specific to stillbirths were absent from the Millennium Development Goals (MDGs) and are still missing in the 2030 Agenda for Sustainable Development. [2]

The United Nations' Global Strategy for Women's, Children's and Adolescents' Health (2016–2030) includes stillbirths in its vision, "An end to preventable maternal, newborn, child and adolescent deaths and stillbirths", and urges for stillbirths to be prioritized. [2] The Every Newborn Action Plan (ENAP), which was endorsed by 194 WHO Member States, calls for each country to achieve a rate of 12 stillbirths or fewer per 1,000 total births by 2030 and to reduce equity gaps, particularly in countries that have already met the stillbirth target. [2, 8]

In Eritrea, stillbirth rate was 18.3 stillbirth per 1000 total birth in 2019.[2] It was reduced by 21.3 % compared to stillbirth estimated in the year 2000. This rate makes Eritrea one of the 56 countries who are at risk of missing the ENAP stillbirth target by 2030. [2]

Risk factors for stillbirth can be due to Socioeconomic and demographic, obstetric and fetal factors. Socioeconomic and demographic factors which is primarily a combination of education, residency, marital status, occupation, income and age had an influence on the still birth rate as showed in different studies. [1, 2, 9-13] A study in rural China showed that paternal exposure to smoking was risk factors of stillbirth. the study also showed that Folic acid intake before and after pregnancy had a protect factors of stillbirth. [14]

Different study showed that preceding birth interval less than 24 month, increasing parity, maternal hypertension or pregnancy induced hypertension, maternal diabetes, maternal obesity, previous history of stillbirth, bleeding during pregnancy, febrile illness during pregnancy, mother with no or inadequate prenatal care, labour length greater or equal to 24 hours, refereed cases, presence meconium and not using partograph were obstetric risk factors associated with stillbirth. [1, 2, 9-20] A study in Nigeria showed that delivery at health facilities was more risky by 81% .[21] the same study also showed that C-section was 46 % more risky than vaginal delivery. Study done by Tesema et al. revealed also C-section was by 81% more risky than counterparts. [11] Different studies showed that fetal factors associated with stillbirths were being male by gender, fetal congenital malformation, and low birth weight or small for gestational age and multiple pregnancies. [2, 9, 12, 17, 19, 20, 22]

Establishing association of stillbirth with different maternal, fetal, pregnancy and obstetric factors can help to prioritize interventions to improve birth outcomes in resource-poor areas, including Eritrea.[23] To the knowledge of the researchers, a similar research has not been done in Eritrea. Research is critical to develop interventions aimed at averting such risk factors of stillbirth. Hence, this study was conducted to identify socio-demographic, maternal health-related and obstetric-related factors that possibly result in stillbirth in the study area.

II. Methodology

a) Study Design

The study was a hospital-based unmatched case-control. Mothers who gave stillbirths were considered as cases whereas those who gave live births were considered as controls. The inclusion criteria were whose with charts available and had all the necessary information.

b) Study area

The study was conducted at Dekemhare Hospital, which is located in Zoba Debub (Southern Region), around 40 km to south east of Asmara, the capital city of Eritrea. This hospital provides service to subzone of Dekemhare, which has a population around 60,000. [24] It also serves as a referral center for three subzones of Southern Region; Segheneyti, Mai-ayni and Tsorona. This hospital comprises several wards such as medical, pediatric, maternity and also dental and ophthalmic clinics. Maternity hospital provides comprehensive emergency, obstetric, and neonatal care service. In addition, the hospital provides maternal waiting room.

c) Study population

All mothers who delivered from January 2017 to December 2021 in Dekemhare Hospital were the study population.

d) Sample Size Determination

Sample size was calculated using Epi-Info 7.0 StatCalc program by taking assumptions of 95% confidence level, three controls for each case, 80% power and 35% prevalence of exposure (birth weight was taken as exposure) among control and odds ratio 1.78. A total sample size of 543 (136 cases and 407 controls) were calculated.

e) Sampling procedure

Consecutive sampling was implemented to recruit all cases in the study area—all stillbirths with complete information were selected. However, to select controls, first, all live births in the hospital with complete information were listed to create a sampling frame, and then simple random sampling technique was applied to enroll those live births.

f) Study Variable

The dependent variable for present study was birth outcome dichotomized in to stillbirth and live birth. And the independent variables were sociodemographic factors (age, residence, occupation, marital status), past and present obstetric history and medical history related factor(gravidity, parity, preceding birth interval, history of stillbirth, hypertensive disorder of pregnancy, premature rupture of membrane), abortion and delivery related factors (mode of admission, partograph use, fetal presentation, cord accident, obstructed labor, labor augmentation, duration of labor, mode of delivery) and fetal related factors (gestational age at birth, birth weight, number of newborns, congenital structure).

III. Data Collection

Data were collected using structured data extraction tool developed from literature related to stillbirth and modified according to the local context by the investigators. The tool consists of several sections

regarding to sociodemographic, maternal health and pregnancy, labor and delivery and birth outcome.

Data collectors identified charts of mothers from card room using medical record numbers and reviewed the history, delivery summery, partograph, decision notes, progress notes, and operation notes and filled in the checklist. Incomplete charts on major variables under study (no information about birth outcome and missing data more than 40 % the variable) were excluded.

a) Data Quality Control and Assurance

Prior to data collection, the data collectors were trained with a practical session for one day on techniques of data collection. Pretest was carried out on 5% of the samples in the same hospital in the years before the study period and modification of the checklist was made on rephrasing and skipping patterns. The investigator reviewed all checklists for omissions, clarity, and consistency of data to verify the completeness of the collected data.

b) Data Analysis

Data were entered in CSPro 7.2 and were analyzed using SPSS version 26 b. Frequency, percentage and odds ratio (crude and adjusted) were used to describe the study population in relation to relevant variables. Univariable and multivariable logistic regression was used to identify characteristics associated with outcome. Variables found to have statistically significant associations with the outcome of interest at univariable analysis were considered in the multivariable analysis. Crude and adjusted odds ratio with 95% CI was calculated and p-value <0.02 and <0.05, respectively, was used to declare statistical significance.

c) Ethical considerations

Ethical clearance was obtained from the Research Ethics and Review Committee of Ministry of Health, and further permission was obtained from offices of the Ministry of Health Debub Zone and Dekemhare Hospital. Patient's confidentiality was kept secured and only selected researchers had an access to the data and personal identifiers were codded and removed from analysis. Consent form was not sought from enrolled individuals as this study was using a secondary data.

IV. Results

During the study period there were 6079 total delivers and 151 stillbirths. Thus, the prevalence of stillbirth during the study period in Dekemhare Hospital was 2.5 % or 25 per 1000 deliveries. Out of 151stillbirths, 13 cases were excluded from the study due to incomplete information. So finally a total of 552 sample charts of mothers who gave birth in Dekemhare Hospital were included in the analysis. Of all stillbirth, 51% were fresh (fetal death during labor and delivery) and 49 % were macerated. (Fig 2) The maternal mean age was 28 years (SD=6.3) and 62% of cases and 78 % of controls were aged between 20 to 34 years. Vast majority of cases (89%) and controls (96%) were married. 59% of cases and 34 % of controls were rural resident. Besides, 91% cases and 95% controls were housewives. (Table 1)

Table 1: Sociodemographic Characteristics of Mothers in Dekemhare Hospital, Jan 2017 to Dec 2021(N=552)

Variables	Category	Cases N (%)	Controls N (%)	Total N (%)
Maternal age	less than 20	11 (8)	21 (5)	32 (5.8)
	20 to 34	85 (62)	321(78)	406 (74)
	above 34	42 (30)	72 (17)	114 (21)
Residency	urban	56 (41)	272(66)	328 (59)
	rural	82 (59)	142 (34)	224 (40)
Marital status	married	123 (89)	398(96)	521(94)
	single	15 (11)	16 (4)	31 (7)
Occupation	house wife	125 (91)	393 (95)	518 (94)
	employed	13 (9)	21 (5%)	34 (6)

a) Maternal Health and Pregnancy Related Characteristics of Participants

More than three-fourths, 78% of cases and 76 % of controls were multigravida and 11% of cases and 8% of controls had previous history of stillbirth. Merely, 4 % of cases and 1% of controls had experienced different medical illness. Regarding birth interval, 17% of cases and 12% of controls had presiding birth interval of less than 2 years. (Table 2)

Table 2: Maternal Health Related Characteristics of Mothers in Dekemhare Hospital, Jan 2017 to Dec 2021(N=552)

Variables	Category	Cases N (%)	Controls N (%)	Total N (%)
Gravidity	Primigravida	31 (23)	99 (24)	130 (24)
	Multigravida	107 (78)	315 (76)	422 (76)
Parity	Primiparos	36 (26)	106 (26)	142 (26)
	Multipara	102 (74)	308 (74)	410 (74)
History of abortion	Yes	30 (22)	83 (20)	113 (21)
	No	78 (57)	236 (57)	314 (57)
Preceding birth interval	< 2 years	18 (17)	47 (12)	65 (12)
	≥ 2 years	89 (83)	268 (65)	357 (65)
History of still birth	Yes	15 (11)	32 (8)	47 (9)
	No	92 (67)	288 (70)	380(69)
Maternal medical illness	Yes	5 (4)	6 (1)	11 (2)
	No	133 (96)	408 (99)	541 (98)

b) Labor and Delivery Related Characteristics of Participants

Almost two third, 65 % of cases and 76 % of controls, were admitted in the first stage of labour. About 38% of cases and 11 % of controls were referred from other health facilities. And around 19 % of cases and 37 % of controls filled in the three components of partograph (fetal condition, progress of labour and maternal condition). Augmentation or induction of labour was conducted in 9 % of cases and in 3 % of controls. In the cases group 5 % had cord accident and 3% had uterine rupture, but none of those were happened among control. Prolonged obstructed labour was experienced in 15 % of cases and 5 % of controls. (Table 3)

Table 3: Labor and Delivery Related Characteristics of Mothers in Dekemhare Hospital, Jan 2017 to Dec 2021(N=552)

Variable	Category	Cases N (%)	Controls N (%)	Total N (%)
Use of partograph	Yes	26 (19)	154 (37)	180 (33)
	No	112 (81)	260 (63)	372 (67)
Prolonged obstructed	Yes	20 (15)	21 (5)	41 (7)
	No	118 (86)	393 (95)	511 (93)
Augment or induced	Yes	12 (9)	11 (3)	23 (4)
	No	126 (91)	403 (97)	529 (96)
Prom	Yes	3 (2)	25 (6)	28 (5)
	No	135 (98)	389 (94)	524 (95)
Duration of labour	Less than 24h	127 (92)	385 (93)	512 (92)
	> or equal 24h	11 (8)	31 (7)	42 (8)
Mode of admission	Referred	52 (38)	46 (11)	98 (18)
	Not referred	86 (62)	368 (89)	454 (82)
Presence of PIH	Yes	4 (3)	1 (0)	5 (1)
	No	134 (97)	413 (100)	547(99)
Presence of cord accident	Yes	7 (5)	1 (0)	8 (1)
	No	131 (95)	413 (100)	544 (99)
Presence of uterine rupture	Yes	4 (3)	0 (0)	4 (1)
	No	134 (97)	414 (100)	548 (99)
Presence of APH	Yes	4 (3)	2 (1)	6 (1)
	No	134 (97)	412 (99)	546(99)
Stage of labour on admission	First stage	89 (65)	315 (76)	404 (73)
	Second stage	49 (35)	99 (24)	148 (27)

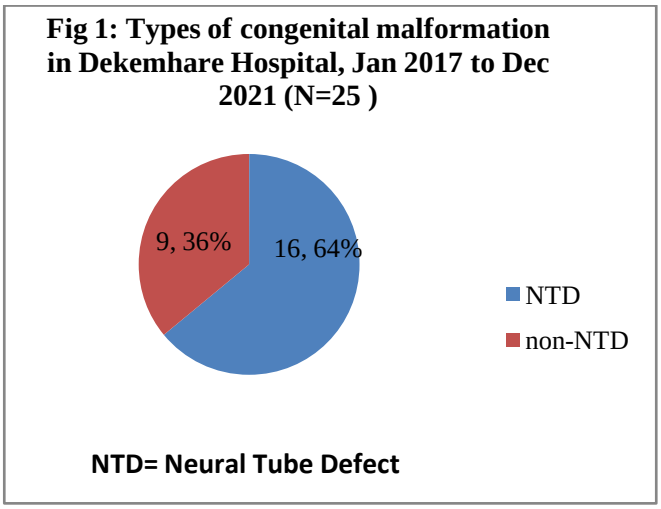
Mode of delivery	cephalic	94 (68)	374 (90)	468 (85)
	Breech delivery	25 (18)	9 (2)	34 (6)
	Cs delivery	19 (14)	31 (8)	50 (9)

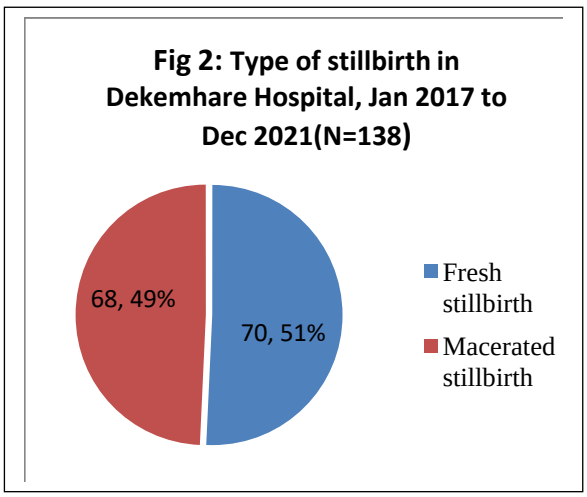
c) *Fetal Related Characteristics of participants*

From a total of 138 cases reviewed, 32 % had positive fetal heart beat on admission. And also 72 % of cases and 89 % of controls delivered in their gestational age between 37 and 42 weeks. Around 49% of cases' babies and 91% of controls' babies had birth weight in the range of 2500-3999 g. Of all deliveries, 59 % of case and 51 % of controls delivered male newborns and also only 6 % of cases and 7% controls had multiple deliveries. Among deliveries 15% of cases and 1 % of controls had fetal congenital malformation. Among all the fetal congenital malformation, 64% were neural tube defects. (Fig 1) The mean birth weight was 2603 (SD=941) gram for case and 3236 (SD=459) gram for controls. And also mean gestational age was 37(SD=3) weeks of the cases and 39(SD=1) weeks for controls.(Table 4)

Table 4: Fetal Related Characteristics in Dekemhare Hospital, Jan 2017 to Dec 2021(N=552)

Variables	Category N (%)	Cases N (%)	Controls N (%)	Total N (%)
Number of fetus	Single	130 (94)	407 (98)	537 (97)
	Twin	8 (6)	7 (2)	15 (3)
Baby gender	Female	56 (41)	204 (50)	260 (47)
	Male	82 (59)	210 (51)	292 (53)
Birth weight	Less 2500	59 (43)	16 (4)	75 (14)
	2500-3999	67 (49)	375 (91)	442 (80)
	Above 4000	12 (9)	23 (6)	35 (6)
Type of stillbirth	Fresh stillbirth	70 5(1)	0 (0)	70 (13)
	Macerated stillbirth	68 (49)	0 (0)	68 (12)
Congenital abnormality	Yes	21 (15)	4 (1)	25 (5)
	No	117 (85)	410 (99)	527 (96)
Gestational age	< 37	35 (25)	31 (8)	66 (12)
	37-42	99 (72)	367 (89)	466 (85)
	>=42	4 (3)	16 (4)	20 (4)
Mean with SD	Birth weight (gram)	2603+941	3236+459	3078+673
	Gestational age (weeks)	37+3	39+1	38+2





d) Determinants of Stillbirth

A univariable analysis was done to assess the association of stillbirth with different independent variables using logistic regression. The result showed that variables like residency, mode of delivery, number of fetus, birth weight, marital status, use of partograph, gestational age, presence of congenital abnormality, presence of prolonged obstructed labour, labour augmentation or induction, mode of admission, presence of PIH and presence of APH have shown statistical association with stillbirth in the univariable analysis (Table 5).

Those variables with a $p<0.2$ in the univariable analysis were considered for model building. A forward selection was used to eliminate insignificant covariates from the final model. Besides, multicollinearity was checked to assess whether covariates had correlation. The results from the final model revealed that, breech (AOR: 10.27; 95%CI: 3.87-27.27), congenital abnormalities (AOR: 9.36; 95%CI: 2.47-35.45), referred from other health facilities (AOR: 4.71; 95%CI: 2.41-9.17), augmented or induced (AOR: 4.79; 95%CI: 1.33-17.31), cord accident (AOR: 75.40; 95%CI: 6.57-865.75) were found be risk factors of stillbirth. Conversely, birth weight 2500-3999 g (AOR: 0.03; 95%CI: 0.01-0.07), above 4000g (AOR: 0.12; 95%CI: 0.04-0.32), utilized partograph (AOR: 0.38; 95% CI: 0.20-0.74), PIH (AOR: 0.03; 95%CI: 0.03-0.36), PROM (AOR: 0.14; 95% CI: 0.03-0.68) were found to be a protective factor of stillbirth. (Table 5)

Table 5: Determinants of Stillbirth among Women Attended Deliveries in Dekemhare Hospital, a univariable and multivariable analysis

Variables	Categories	COR (95%CI)	AOR (95%CI)
Residence	Rural	1	
	Urban	0.35 (0.24-0.53)*	
Mode of delivery	Cephalic	1	1
	Breech	11.11 (5.02-24.60)*	10.27 (3.87-27.27)**
	CS	2.45 (1.33-4.53)*	1.74 (0.75-4.05)
Number of fetus	Multiple	1	
	Single	0.28 (0.10-0.78) *	
Birth weight	<2500	1	1
	2500-3999	0.05 (0.03-0.09) *	0.03 (0.01-0.07)**
	4000+	0.14 (0.06-0.35) *	0.12 (0.04-0.32)**
Marital status	Married	1	
	Single	0.33 (0.15-068) *	
Use of partograph	No	1	1
	Yes	0.39 (0.25-0.63) *	0.38 (0.20-0.74)**
Gestational age	<37	1	
	37-42	0.24 (0.14-0.40) *	
	>=42	0.22 (0.07-0.73) *	
Congenital abnormality	No	1	1
	Yes	18.49 (6.22-54.92) *	9.36(2.47-35.45)**
Prolonged obstructed	No	1	
	Yes	3.19 (1.67-6.08) *	
Augmentation or induced labour	No	1	1
	Yes	3.51 (1.51-8.14) *	4.79 (1.33-17.31)**
Mode of admission	not referred	1	1
	referred	4.86 (3.07-7.71) *	4.71 (2.41-9.17)**
Presence of PIH	No	1	1
	Yes	12.39 (1.37-111.80) *	0.03 (0.03-0.36)**
Presence of cord accident	No	1	1
	Yes	22.18 (2.70-181.90) *	75.40 (6.57-865.75)**

PROM	No	1	1
	Yes	0.35 (0.10-1.17) *	0.14 (0.03-0.68)**

*Notes: * COR significant at P-value <0.2, ** AOR significant at P-value <0.05.*
1=Reference

V. Discussion

According to the findings of this study prevalence of stillbirth was 2.5 %. The prevalence of stillbirth was almost consistent with a study conducted in South India and Bangladesh, which shows 2.97% and 2.6% respectively.[20, 25]Nonetheless, it was higher than studies done in India, Saudi Arabia, and Nepal.[10, 12, 26-28] Beside, it was lower than studies in Nigeria (12.4%), Aksum (3.68%), Nigerian referral hospital (3.96%) and tertiary hospital Nigerdelta (4.8%).[1, 21, 29, 30]

In this study breech delivery was significantly associated with stillbirth compared to cephalic delivery. This result was in agreement with findings in various studies. [26, 30-32] so, breech presentation needs Closer surveillance and appropriate management to prevent stillbirth.

The odds of having stillbirth were higher in those delivered with fetal congenital abnormalities than without congenital abnormality in this study. This finding was consistent with studies done in other setting. [20, 27, 28, 33]. This could be explained by a lack of maturity of the vital organs for fetal survival making the fetus disposed to fatal complications and death. There is belief that continuing stillbirths are inevitable, and mostly due to non-preventable congenital abnormalities, but not all congenital abnormalities are inevitable, like neural tube defect could be prevented through folic acid supplementation.

This study found that women who referred from other facilities had more risk to have stillbirth than counterparts. This finding was in agreement with similar study findings at Nigeria, Southeast Ethiopia, and India. [17, 26, 29] This can be explained by most of the referred mothers coming from peripheral health facilities with serious complications. And also the distance to reach the hospitals to which they were referred pays to delay in receiving care, which can obviously cost the life of their fetus.

The odds of experiencing stillbirth were higher among mothers who had labour augmented or induced than their counterparts. This finding is consistent with the findings of studies in Ethiopia and India,. [22, 34] But a study in Nepal revealed that Women with augmentation of labor had no increased risk of stillbirth. [35]

In the present study stillbirth was higher among mothers with umbilical cord accident than those without umbilical cord accident. This is in line with a study by Collins. [36] This could be due to compromised blood circulation to the fetus, which leads to hypoxia and death. This indicates that, now it is time to focus on screening and managing umbilical cord accident prenatally.

According to the finding of this study, giving birth to a baby weighing above 2500gm was found to be a protective a factor associated with stillbirth. This finding is in line with studies done in Ghana, Ethiopia, Nepal, Nigeria, Southwestern Ethiopia and Southeast Ethiopia. [12, 17-19, 30, 34, 37] This could be due to the fact that low birth weight is a complicated public health problem that includes long-term maternal malnutrition, ill health, and poor health care during pregnancy; which all can result in immature newborn and stillbirth.

This study yielded that those mothers whose labour was followed by partograph had reduced stillbirth than those not followed by partograph. This result was consistent with studies in Ethiopia, Aksum General Hospital and Nepal, that showed increased risk of stillbirth if the partograph was not used.[1, 10, 34]Poor partograph utilization may resulted in prolonging second stage of labor which could also result in miserable interventions like cesarean section, augmentation and instrumental delivery.[1]

In this study pregnancy induced hypertension showed protective effect. The current study's finding was consistent with study done in Japan, which showed PIH has a protective to stillbirth.[38]However, this finding was inconsistent to studies in several settings. [9, 13, 14, 37, 39-43] This is probably because infants are delivered early due to maternal reasons, which reduces the stillbirth risk before the disease becomes symptomatic. [38] The presence of PROM was found to be a protective factor for stillbirth. This finding was in contrast to study done in Ethiopia, which showed PROM was a risk factor for stillbirth. [34] Nonetheless, another study showed a non-significant effect of early rupture of membrane on stillbirth. [44]

VI. Limitation of the Study

The study was institution based study that can't be generalized to other settings. The study did not assess the effect of ANC attending and number of visits due to its absence in the documentation that could have an effect on results. Since this study was solely retrospective, it was opened to bias and results may be affected. Finally, this study did not explore the quality of care given in the health facility that requires advanced investigation which may have contribution to additional risk factors for stillbirth. So, further prospective study is needed to address these issues.

VII. Conclusion

The factors that negatively affected stillbirth were not use of partograph, low birth weight, being referred from other health facility, labour augmentation or induction, presence of fetal congenital malformation, and presence of cord accident. Conversely, presence of PIH and PROM had a protective effect of stillbirth.

Based on this study, we highly recommended on the improvement of health care provider's skill to manage babies presenting in breech position, utilization of partograph during labour, strengthening referral system and monitoring and evaluating of referral practice, improving documentation of antenatal care visits in delivery register. And also timely and early identification of mothers who are at risk for neural tube defect and supplementation of folic acid at preconception.

Author Contributions: HG, FK and BT contributed to the study conception and design. Material preparation, data collection and analysis were performed by all authors. All the authors reviewed the manuscript and approved the final version of the manuscript.

Funding: This research had no any source of fund.

Disclosure

Abbreviations: PROM: Premature Rupture of Membrane; PIH: Pregnancy Induced Hypertension; CS: Cesarean Section; APH: Antepartum Haemorrhage

Acknowledgments

Authors acknowledges to the data collectors and Dekemhare hospital.

Conflict of interest: The authors report no conflicts of interest in this work.

References Références Referencias

1. Berhe et al: Prevalence and determinants of stillbirth among women attended deliveries in Aksum General Hospital: a facility based cross-sectional study. BMC Res Notes 2019, 12(368).
2. United Nations Inter-agency Group for Child Mortality Estimation (UN IGME): A Neglected Tragedy: The global burden of stillbirths', United Nations Children's Fund, New York, 2020.
3. Lucia Hug et al: Global, regional, and national estimates and trends in stillbirths from 2000 to 2019: a systematic assessment. Lancet 2021, 398: 772–785.
4. Sethi et al: Assessment of knowledge of evidence-based maternal and newborn care practices among midwives and nurses in six provinces in Indonesia. Int J Gynecol Obstet 2019, 144 (Suppl. 1): 51 –58.
5. WHO, UNICEF: ENDING PREVENTABLE NEWBORN DEATHS AND STILLBIRTHS BY 2030: MOVING FASTER TOWARDS HIGH-QUALITY UNIVERSAL HEALTH COVERAGE IN 2020–2025. 2020.
6. Darmstadt et al: Reducing stillbirths: interventions during labour. BMC Pregnancy and Childbirth 2009, 9(56).
7. Joint Technical Brief on Stillbirth Situation and Way Forward for the East Mediterranean, Arab States, and Middle East & North Africa Region. Amman/Cairo: World Health Organization Regional Office for the Eastern Mediterranean (WHO EMRO), United Nations Population Fund Arab States Regional Office (UNFPA ASRO), United Nations Children's Fund Regional Office for the Middle East & North Africa (UNICEF MENARO), 2021.
8. WHO: Global Strategy for Women's, Children's and Adolescents' Health (2016–2030): early childhood development. 2018.
9. Almeida MF et al: Risk-factors for antepartum fetal deaths in the city of São Paulo, Brazil. Rev Saúde Pública 2007, 41(1): 35-43.
10. KC et al: Inadequate fetal heart rate monitoring and poor use of partogram associated with intrapartum stillbirth: a case-referent study in Nepal. BMC Pregnancy and Childbirth 2016, 16(233).
11. Tesema et al: Prevalence of stillbirth and its associated factors in East Africa: generalized linear mixed modeling. BMC Pregnancy Childbirth 2021, 21(414).
12. Hirst et al: The antepartum stillbirth syndrome: risk factors and pregnancy conditions identified from the INTERGROWTH-21st Project. BJOG 2018, 125: 1145–1153.
13. Lakshmi ST et al: Risk factors for still birth: a hospital based case control study. Int J Reprod Contracept Obstet Gynecol 2017, 6:970-974.
14. Yimin Qu, Shi Chen, Hui Pan, Huijuan Zhu, Chengsheng Yan, Shikun Zhang, Yu Jiang: Risk factors of stillbirth in rural China: A national cohort study. SCIENTIFIC REPORTS 2019, 9(365).
15. Robert M. Silver et al: Causes of Death among Stillbirths. JAMA 2011, 306(22): 2459–2468.
16. WHO: Making every baby count: audit and review of stillbirths and neonatal deaths. 2016.
17. Mekonnen Dagne, et al: Determinants of Stillbirth among Deliveries Attended in Bale Zone Hospitals, Oromia Regional State, Southeast Ethiopia: A Case–Control Study. International Journal of Women's Health 2021, 13: 51–60.
18. Nonterah EA, Agorinya IA, Kanmiki EW, Kagura J, Tamimu M, Ayamba EY et al: Trends and risk factors associated with stillbirths: A case study of the Navrongo War Memorial Hospital in Northern Ghana. PLoS ONE 2020, 15(2).
19. Welegebriel et al: Determinants of stillbirth in Bonga General and Mizan Tepi University Teaching Hospitals southwestern Ethiopia, 2016: a case–control study. BMC Res Notes 2017, 10(713).

20. Rajshekher V. Mali et al: Association of Stillbirths with Maternal and Fetal Risk Factors in a Tertiary Care Hospital in South India. Obstetrics and Gynecology International 2021.
21. Njoku C.O, Emechebe C.I, Eyong E.M, Ukaga J.T, Anachuna K.C: Prevalence and risk factors for stillbirths in a tertiary hospital in Niger Delta area of Nigeria: a ten year review. Int J Med Biomed Res 2016, 5(3): 106-113.
22. Newtonraj et al: Level, causes, and risk factors of stillbirth: a population-based case control study from Chandigarh, India. BMC Pregnancy and Childbirth 2017, 17(371).
23. Flenady et al: An evaluation of classification systems for stillbirth. BMC Pregnancy and Childbirth 2009, 9: 24 2009, 9(24).
24. Hospital Dekemhare: DEKEMHARE SUB ZONE ANNUAL HEALTH REPORT, 2020
25. S. Nahar et al: Factors Influencing Stillbirth in Bangladesh: A Case–Control Study. Paediatric and Perinatal Epidemiology 2013, 27:158–164.
26. Dandona et al: Deferred and referred deliveries contribute to stillbirths in the Indian state of Bihar: results from a population-based survey of all births. BMC Medicine 2019, 17(18).
27. E. I. Archibong et al: Antenatal intrauterine fetal death: a prospective study in a tertiary hospital in south-western Saudi Arabia. Journal of Obstetrics and Gynaecology 2003, 23(2):170–173.
28. Jahani M et al: Factors Affecting Stillbirth Rate in the Hospitals Affiliated to Babol University of Medical Sciences. Iranian Journal of Neonatology 2015, 6(3).
29. Banke- Thomas A AC, Gwacham- Anisiobi U, et al.: Influence of travel time and distance to the hospital of care on stillbirths: a retrospective facility- based cross- sectional study in Lagos, Nigeria. BMJ Global Health 2021, 6.
30. Okonofua et al: Prevalence and determinants of stillbirth in Nigerian referral hospitals: a multicentre study. BMC Pregnancy and Childbirth 2019, 19(533).
31. Macharey, Georg et al: Breech presentation at term and associated obstetric risks factors-a nationwide population based cohort study. Arch Gynecol Obstet 2017, 295: 833–838.
32. L. Zsirai et al: Breech presentation: its predictors and consequences. An analysis of the Hungarian Tauffer Obstetric Database (1996–2011). Acta Obstet Gynecol Scand 2016, 95: 347–354.
33. Tesfay N, Legesse F, Kebede M and Woldeyohannes F: Determinants of stillbirth among reviewed perinatal deaths in Ethiopia. Front Pediatr 2022, 10(1030981).
34. Liyew et al: Risk Factors of Stillbirth among Women Who Gave Birth in Amhara Region Referral Hospitals, Ethiopia, in 2019: A Case-Control Study. International Journal of Women's Health 2021, 13.
35. Litorp H, Sunny AK, Kc A.: Augmentation of labor with oxytocin and its association with delivery outcomes: A large-scale cohort study in 12 public hospitals in Nepal. Acta Obstet Gynecol Scand 2021, 100:684–693.
36. Collins: Umbilical cord accidents.BMC Pregnancy and Childbirth 2012, 12.
37. KC et al: Risk factors for antepartum stillbirth: a case-control study in Nepal. BMC Pregnancy and Childbirth 2015, 15(146).
38. ReiHaruyam et al: Causes and risk factors for singleton stillbirth in Japan: Analysis of a nationwide perinatal database, 2013–2014. SCIENTIFIC REPORTS 2018, 8(4117).
39. Neogi et al: Risk factors for stillbirths: how much can a responsive health system prevent? BMC Pregnancy and Childbirth 2018, 18(33).
40. Abebe H, Shitu S, Workye H, Mose A: Predictors of stillbirth among women who had given birth in Southern Ethiopia, 2020: A case-control study.PLoS ONE 2021, 16(5).
41. Ananth and Basso: Impact of Pregnancy-Induced Hypertension on Stillbirth and Neonatal Mortality in First and Higher Order Births: A Population-Based Study. Epidemiology 2010 January, 21(1): 118–112.
42. Tao Xiong et al: hypertensive disorders in pregnancy and the stillbirth rate: a facility-based study in China. Bull World Health Organ 2018, 96: 531–539.
43. Berhe et al: Effect of pregnancy induced hypertension on adverse perinatal outcomes in Tigray regional state, Ethiopia: a prospective cohort study. BMC Pregnancy and Childbirth 2020, 20(7).
44. Yezengaw YT et al: Stillbirth and its Association with Early Rupture of Membranes in Sub-Saharan Africa: Systematic Review and Meta-Analysis. J Gen Pract 2022, 10(3).

This page is intentionally left blank

Global Journal of Medical Research: E
Gynecology and Obstetrics
Volume 23 Issue 1 Version 1.0 Year 2023
Type: Double Blind Peer Reviewed International Research Journal
Publisher: Global Journals
Online ISSN: 2249-4618 & Print ISSN: 0975-5888

A Study to Find Out the Efficacy of Strip Immunoassay Test for Insulin Like Growth Factor Binding Protein-1 in Amniotic Fluid for Detection of Premature Rupture of Membranes

By Dr. Akansha Kumawat, Dr. Pushpa Nagar, Dr. Sana Tak, Dr. Aditi Bansal & Dr. Bhavini

Abstract- *Background:* It is an obstetric conundrum which is poorly defined with an obscure etiology, difficulty in diagnosis, association with significant maternal and neonatal morbidity and mortality, with diverse and controversial management strategies.

Aim and Objectives: To know the efficacy of strip immunoassay test in amniotic fluid for detection of premature rupture of membranes.

Materials and Methods: A hospital based observational study carried out on 60 pregnant women attending emergency and OPD with complaints of leaking per vaginum. Strip immunoassay test was performed on all the participants along with a conventional method like ferning and the results obtained were analysed for calculating the diagnostic accuracy of the test.

Keywords: *premature rupture of membranes, ferning, strip immunoassay test, insulin like growth factor binding protein-1.*

GJMR-E Classification: *DDC Code: 618.2 LCC Code: RG524*

Strictly as per the compliance and regulations of:

A Study to Find Out the Efficacy of Strip Immunoassay Test for Insulin Like Growth Factor Binding Protein-1 in Amniotic Fluid for Detection of Premature Rupture of Membranes

Dr. Akansha Kumawat [α], Dr. Pushpa Nagar [σ], Dr. Sana Tak [ρ], Dr. Aditi Bansal [ω] & Dr. Bhavini [¥]

Abstract- Background: It is an obstetric conundrum which is poorly defined with an obscure etiology, difficulty in diagnosis, association with significant maternal and neonatal morbidity and mortality, with diverse and controversial management strategies.

Aim and Objectives: To know the efficacy of strip immunoassay test in amniotic fluid for detection of premature rupture of membranes.

Materials and Methods: A hospital based observational study carried out on 60 pregnant women attending emergency and OPD with complaints of leaking per vaginum. Strip immunoassay test was performed on all the participants along with a conventional method like ferning and the results obtained were analysed for calculating the diagnostic accuracy of the test.

Results: Out of 60 participants (N=60), 38 had PROM (Premature Rupture of Membranes) and; strip immunoassay test was able to diagnose PROM in 34 women with a sensitivity, specificity, positive predictive value ,negative predictive value and diagnostic accuracy of 90%, 91%, 94%, 83% and 90% respectively.

Conclusion: The present study shows that the strip immunoassay test using IGFBP-1 (insulin like growth factor binding protein-1) on the cervicovaginal fluid is an accurate method to diagnose premature rupture of membranes.

Keywords: premature rupture of membranes, ferning, strip immunoassay test, insulin like growth factor binding protein-1.

I. Introduction

Premature rupture of membranes (PROM) refers to rupture of fetal membranes prior to the onset of labour, regardless of the gestational age. It is seen in 10% of term pregnancies and 2- 4% of preterm pregnancies [(1)].

Diagnosis of rupture of membranes depends on documentation of three clinical signs on sterile speculum examination: - 1) Visual pooling of fluid in the posterior fornix of vagina or leakage of fluid from the cervical os; (2) An alkaline pH of the cervicovaginal discharge; and (3) Microscopic ferning pattern of the cervicovaginal discharge on drying (fern test)[(2)].

Because of the limitations with the current gold standard for the diagnosis of premature rupture of membranes such as- 1)invasiveness 2)risk of chorioamnionitis and 3)pregnancy loss with intra amniotic dye instillation, 4)long duration of leaking leading to non-visualization of pooling of fluid in the vagina and 5)alkaline pH of the cervicovaginal fluid in conditions other than leaking, investigators have long been searching for an alternative and more objective test with a good diagnostic accuracy which are primarily based on the identification of one or more biochemical markers in the cervicovaginal discharge like Insulin like growth factor binding protein-1 (IGFBP-1), Alpha FetoProtein, Placental Alpha Microglobulin(PAMG-1), prolactin, HCG, Urea and creatinine etc. that are present in the setting of rupture of membranes, but absent in women with intact membranes.

The present study has been perpetrated to find out the efficiency of strip immunoassay test for insulin like growth factor binding protein-1 in amniotic fluid so that timely obstetric intervention can be done to minimise the feto-maternal risk, especially in a low resource setting.

II. Aim and Objectives

The aim of the study is to know the efficacy of detection of premature rupture of membranes by strip immunoassay test by detecting insulin like growth factor binding protein-1 (IGFBP-1) in amniotic fluid.

The objective of the present study is to assess the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of strip immunoassay test on amniotic fluid to diagnose PROM.

III. Material and Methods

The study was conducted in the Department of Obstetrics and Gynaecology of SMS Medical College, Jaipur. Pregnant women attending OPD and emergency with complaints of leaking per vaginum were included in

Author α ρ ¥: Resident, Department of Obstetrics and Gynaecology, SMS Medical College, Jaipur. e-mail: akanshakumawat95@gmail.com
Author σ: Senior Professor, Department of Obstetrics and Gynaecology, SMS Medical College, Jaipur.
Author ω: Associate Professor, Department of Obstetrics and Gynaecology, SMS Medical College, Jaipur.

the study with written informed consent. A detailed history and thorough examination and routine investigations were done. Sterile per speculum examination to detect amniotic fluid pooling through cervical canal was done. In all cases both Strip immunoassay test for insulin like growth factor binding protein-1 test and Fern test were performed. *Strip immunoassay test for insulin like growth factor binding protein-1-* sample of leaking fluid was taken by speculum examination by keeping a polyester swab stick in posterior vaginal fornix for about 10 second and swab was then rinsed in a buffered solution for about 5 seconds, yellow area of the dipstick provided in the kit was placed in the tube for 20 seconds then removed and placed on a flat surface. The stick contains monoclonal antibodies to insulin like growth factor binding protein-1 and absorbs the extracted specimen. If the extracted sample contains insulin like growth factor binding protein-1 in the extracted sample, two blue lines appeared on the stick. It meant test was positive, if no blue line was seen up to 5 min then test was negative. *Fern test–* sample of leaking fluid taken by speculum examination with a swab placed in posterior vaginal fornix and spread on a slide. Then the slide was dried and examined under low power microscope for crystallization of amniotic fluid to form fern like pattern which was considered as positive test.

The diagnostic values of the tests were determined by calculating sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy.

IV. Statistical Analysis

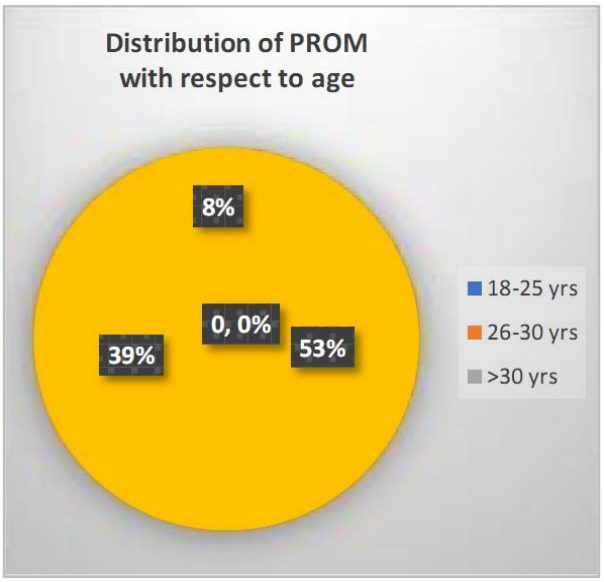
Data was summarized and entered in MS Excel sheet. Continuous variables were summarized as mean and standard deviation were analyzed by using unpaired t test. Nominal / categorical variables were summarized as proportions and were analyzed by using chi-square/ Fischer exact test, p-value$<$0.05 was taken as significant. The diagnostic value of the tests will be determined by calculating sensitivity, specificity, positive predictive value and negative predictive value and diagnostic accuracy and comparisons made. p-value $<$0.05 will be taken as significant.

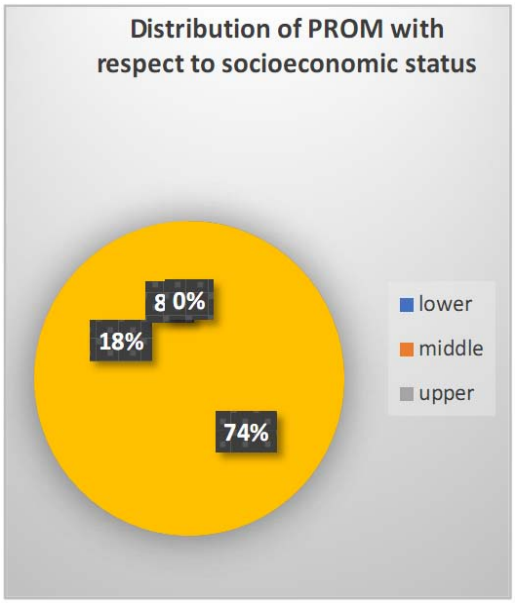
V. Observations and Discussions

In present study, among women who had complaints of leaking PV (n=60) on examination, 35 of the participants had leaking Per vaginum and 25 did not have leaking per vaginum. On further examination, it was found that out of 25, 3 had membranes ruptured (PROM-Present) and 22 had membranes intact (PROM-absent). So, 38 participants had ruptured membranes and the rest 22 had intact membranes. Out of these 38, 34 were diagnosed by Strip immunoassay test for insulin like growth factor binding protein-1 and only 18 were ferning Positive.

Table 1

Age	Ruptured membranes	Membranes intact	p value- 0.563
18-25 yrs	20 (52.6%)	13 (59.1%)	
26-30 yrs	15 (39.5%)	9 (40.9%)	
>30 yrs	3 (7.9%)	0(0.0%)	
Residence	Ruptured membranes	Membranes intact	p value- 0.554
Urban	16 (42.1%)	11 (50.0%)	
Rural	22 (57.9%)	11 (50.0%)	
Socioeconomic status	Ruptured membranes	Membranes intact	p value- 0.014
Upper	3 (7.9%)	1 (4.5%)	
Middle	7 (18.4%)	12 (54.5%)	
Lower	28 (73.7%)	9 (40.9%)	





In present study, the mean age (years) in PROM cases was 25.66 ± 4.31. In a similar study by Evrim Erdemoglu et al[3] and Abdelazim et al[4] the mean age of participants with PROM was 25.6 ± 5.5 years and 31.5 ± 9.52 years respectively. There was no statistically significant difference between women with ruptured membranes and intact membranes with respect to age group. 42.1% of women with PROM were from rural areas and 57.9% were from urban areas. There was no significant difference between the two groups in terms of distribution of residence (p = 0.554). Further studies are required to investigate the common occurrence of PROM in rural population. Majority (73.7%) of the participants who had ruptured membranes belonged to lower Socioeconomic Status and the majority (54.5%) of them who had intact membranes belonged to middle socioeconomic status. The present study suggested that occurrence of PROM was more common in women belonging to lower socioeconomic status and it was statistically significant (p=0.014). In a study by Spinillo et al[5], low social class was a significant risk factor for preterm PROM.

Table 2: Association between 'Ferning' and 'Duration Of Leaking (Hours):

Duration of Leaking (Hours)	Ferning		P value
	Positive	Negative	0.022
Mean (SD)	4.72	7.64	
Duration of Leaking (Hours)	Strip immunoassay test		P value
	Positive	Negative	0.010
Mean (SD)	5.53	8.62	

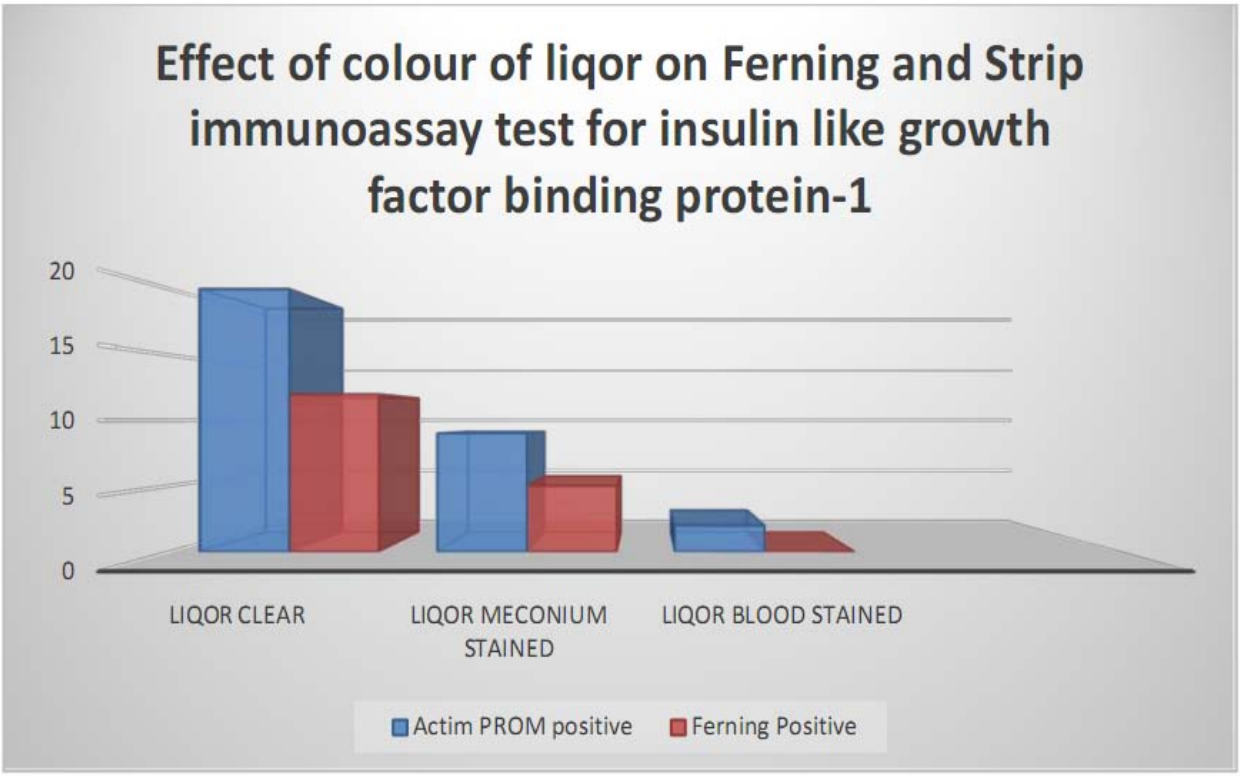
In Table 2, The mean (SD) of duration of leaking in hours in the Strip immunoassay test for insulin like growth factor binding protein-1 Positive Group was 5.53, Strip immunoassay test for insulin like growth factor binding protein-1 negative group was 8.62 whereas that in the Ferning Positive group was 4.72 and Ferning Negative Group was 7.64. Both values were significant but Strip immunoassay test for insulin like growth factor binding protein-1 can detect ruptured membranes of longer duration than Ferning.IGFBP-1 has been shown to be degraded by proteases in the vagina and it has been reported as being unreliable if > 12 hours have elapsed from the time of membrane rupture[6], however, In the present study Strip immunoassay test for insulin like growth factor binding protein-1 could even diagnose 2 cases who had leaking of more than 12 hours.

Table 3: Effect of Colour of liqor on Ferning and Strip immunoassay test for insulin like growth factor binding protein-1:

Ferning	Colour of Liqor		
	Clear	Meconium	Blood Stained
Positive	12	5	0
Negative	11	5	2
Actim PROM	**Colour of Liqor**		
	Clear	Meconium	Blood Stained
Positive	20	9	2
Negative	3	1	0

Upon performing both the tests on all the participants, the following results were obtained:

a. Among the participants who had clear liqor, Ferning test was Positive in 52.2% whereas 87.0% of the participants had STRIP IMMUNOASSAY TEST FOR INSULIN LIKE GROWTH FACTOR BINDING PROTEIN-1 Positive.
b. Among the participants who had liquor meconium stained, 50.0% of the participants gave positive ferning whereas 90.0% of the participants had Strip immunoassay test for insulin like growth factor binding protein-1 Positive.
c. Among those who had liquor blood stained no participants had positive ferning whereas all the participants had positive Strip immunoassay test for insulin like growth factor binding protein-1 test.



To demonstrate the presence of amniotic fluid in the vagina, test results should not be influenced by the contamination of blood, urine, seminal fluid or cervical mucus and meconium. Rutanen et al[7] have reported that the IGFBP1 concentration in urine and seminal fluid are significantly lower than that in serum. And even if amniotic fluid is contaminated by blood, the contamination is negligible, because the serum: amniotic fluid ratio of IGFBP-1 concentration is substantially high. Also, ferning may give false-positive results due to fingerprints, contamination with semen and cervical mucus as well as false negative results due to technical error where a dry swab is used to collect the sample or contamination with blood[8,9,10].

Table 4: Association between Amniotic Fluid Index with Ferning and Strip immunoassay test for insulin like growth factor binding protein-1:

Ferning	AFI		
	<5 cm	5-20 cm	P value- 0.004
Positive	15	3	
Negative	18	24	
Strip immunoassay test for insulin like growth factor binding protein-1 p value <0.001			
Positive	30	6	
Negative	3	21	

In present study, mean AFI (cms) in women with PROM and without PROM were 2.74 (1.46) and 8.91±2.14, respectively. AFI<5 cm was seen in 84.2% women with ruptured membranes and 4.5% of the participants with intact membranes. Our study observed that women with PROM had a decreased AFI, which was statistically highly significant (p<0.001). Similar findings were observed in a study by Erdemoglu E et al[3].

Also, in this study, it was found that the participants who had AFI <5 cm, Strip immunoassay test for insulin like growth factor binding protein-1 was found to be positive in 30 cases whereas, Ferning was positive only in 15 cases (p value-0.004) which was significant with both the testing methods but more significant with Strip immunoassay test for insulin like growth factor binding protein-1.

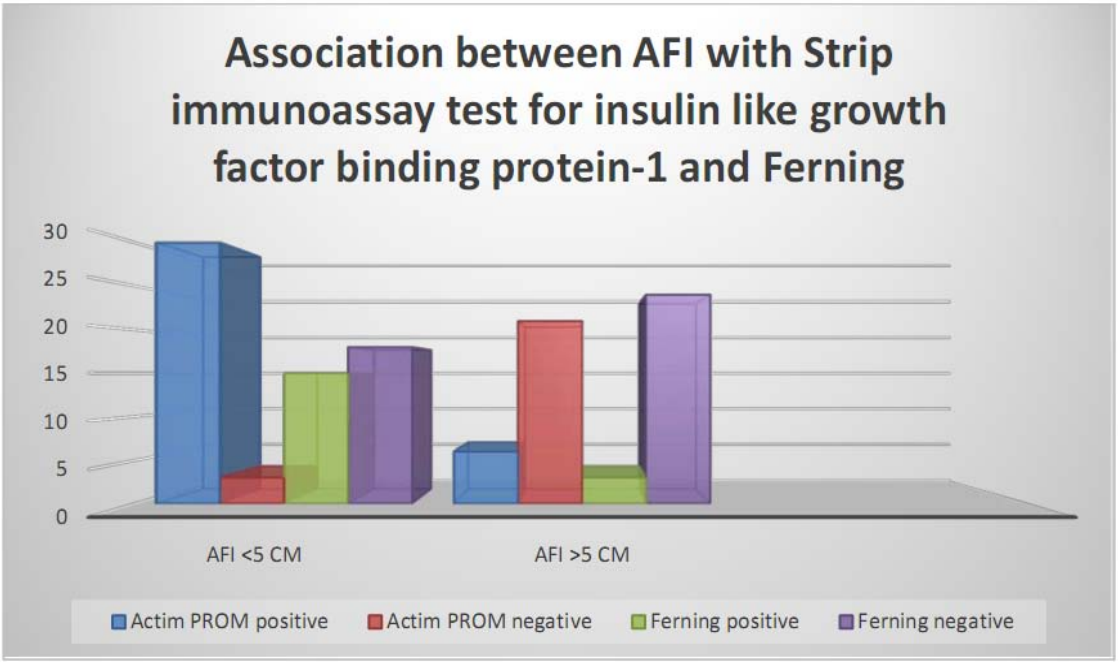


Table 5: The comparison between efficacies of both the tests in our study

VARIABLE	STRIP IMMUNOASSAY TEST	FERNING
Sensitivity	90%	47%
Specificity	91%	100%
Positive Predictive Value	94%	100%
Negative Predictive value	83%	52%
Diagnostic Accuracy	90%	67%

VI. Conclusions and Recommendations

PROM is one of the most troublesome issues in today's obstetrics. Our data shows that IGFBP-1 is an ideal marker of Amniotic fluid and that rapid, simple test for the measurement of this protein in vaginal secretion by a dipstick method has a diagnostic potential in the diagnosis or exclusion of rupture of fetal membranes. The high sensitivity, specificity, PPV, NPV of strip immunoassay test using IGFBP-1 (Strip immunoassay test for insulin like growth factor binding protein-1) makes it a useful test when in doubt of PROM. It is easily performed in clinical setting and no extra staff is required.

The correct diagnosis of PROM is critical for both maternal and foetal concerns, it's high sensitivity and specificity will not only protect the mother from the deleterious effects of intraamniotic infections, post-partum infections and endometritis, but will also prevent the preterm birth by unnecessary induction of labor or cesarean section thus decreasing the burden of neonatal ICU admissions, thereby reducing the maternal morbidity and neonatal mortality and morbidity.

Informed Consent Statement: All subjects here were already informed and gave consent.

Provenance and Peer Review: not commissioned, externally peer-reviewed.

Declaration of Competing Interest: None.

Acknowledgement

The authors would like to thank everyone who supported and assisted throughout all aspects of our study and for their help in writing the manuscript.

Bibliography

1. Mercer BM, Goldenberg RL, Meis PJ, et al. The Preterm Prediction Study: prediction of preterm premature rupture of membranes through clinical findings and ancillary testing. The National Institute of Child Health and Human Development Maternal–Fetal Medicine Units Network. Am J ObstetGynecol2000; 183: 738–745.
2. Caughey AB, Robinson JN, Norwitz ER. Contemporary diagnosis and management of preterm premature rupture of membranes. Rev ObstetGynecol 2008; 1(1): 11–22.
3. Erdemoglu E, Mungan T. Significance of detecting insulin like growth factor binding protein-1 in cervicovaginal secretions: comparison with nitrazine test and amniotic fluid volume assessment. Acta ObstetGynecolScand2004; 83: 622– 626.
4. Abdelazim, Ibrahim A. "Insulin-like growth factor binding protein-1 (Strip immunoassay test for insulin like growth factor binding protein-1 test) for detection of premature rupture of fetal membranes." *The journal of obstetrics and gynaecology research* vol. 40, 4 (2014): 961-7. doi:10.1111/jog.12296
5. A. Spinillo, S. Nicola, G. Piazzi, K. Ghazal, L. Colonna, F. Baltaro: Epidemiological correlates of preterm premature rupture of membranes, Int. J. Gynecol. Obstet.1994; 47: 7-15.
6. College of Obstetricians and Gynecologists, authors. Obstetrician and Premature Rupture of Membranes. Washington, DC: American College of Gynecologists; 1998. (ACOG Practice Bulletin No. 1).
7. Kallioniemi, H, Rahkonen, L, Heikinheimo, O, Stefanovic, V, Paavonen, J. Usefulness of the insulin-like growth factor binding protein-1 bedside test for ruptured fetal membranes. *Acta ObstetGynecolScand* 2014; 93: 1282– 1289.
8. Friedman ML, McElin TW. Diagnosis of ruptured fetal membranes. Clinical study and review of the literature. Am J ObstetGynecol1969; 104: 544–550.
9. Rosemond RL, Lombardi SJ, Boehm FH. Ferning of amniotic fluid contaminated with blood. Obstet Gynecol. 1990; 75: 338-340.
10. Mercer BM. Preterm rupture of the membranes: diagnosis and management. Clin Perinatol2004; 31: 765–782.

Global Journal of Medical Research: E
Gynecology and Obstetrics
Volume 23 Issue 1 Version 1.0 Year 2023
Type: Double Blind Peer Reviewed International Research Journal
Publisher: Global Journals
Online ISSN: 2249-4618 & Print ISSN: 0975-5888

Tubal Re-Anastomoses through a Mini-Laparotomy Incision

By Dr. Ashok R Anand, Dr. Aditi R Jain, Dr. Pushpa Gowda
& Dr. Adithi Jayaprakash

Abstract- *Objective:* To assess the feasibility and reproducibility of tubal anastomosis through a mini-laparotomy incision.

Design: Descriptive case study.

Setting: Academic medical center.

Patient(s): Sixteen patients with previous tubal sterilization who requested tubal re-anastomosis.

Intervention(s): Systematization of the operative steps for tubal re-anastomosis using a mini-laparotomy incision.

Main Outcome Measure(s): Primary outcome measures were feasibility and reproducibility; secondary measures were tubal patency, operative time, complications, and ergonomic qualities.

Keywords: *microsurgery, tubal anastomosis, mini laparotomy, tuboplasty.*

GJMR-E Classification: *NLMC Code: WP 660*

Strictly as per the compliance and regulations of:

Tubal Re-Anastomoses through a Mini-Laparotomy Incision

Dr. Ashok R Anand [α], Dr. Aditi R Jain [σ], Dr. Pushpa Gowda [ρ] & Dr. Adithi Jayaprakash [ω]

Abstract- *Objective:* To assess the feasibility and reproducibility of tubal anastomosis through a mini-laparotomy incision

Design: Descriptive case study.

Setting: Academic medical center.

Patient(s): Sixteen patients with previous tubal sterilization who requested tubal re-anastomosis.

Intervention(s): Systematization of the operative steps for tubal re-anastomosis using a mini-laparotomy incision

Main Outcome Measure(s): Primary outcome measures were feasibility and reproducibility; secondary measures were tubal patency, operative time, complications, and ergonomic qualities.

Result(s): The 31 tubes were successfully re-anastomosed and patency was confirmed. The mean surgical time was 15 minutes per tube.

Conclusion(s): Tubal re-anastomosis after tubal sterilization can be performed through a mini-laparotomy incision. Systematization of the operative steps allowed the performance of the operation at a speed. Larger series and follow-up are needed to assess postoperative pregnancy rates.

Keywords: microsurgery, tubal anastomosis, mini laparotomy, tuboplasty.

I. Introduction

Female sterilization is the most accepted method of birth control. Out of permanent sterilizations, 98% are female sterilizations. It is an important constituent of The National Family Planning Program in India. According to NFHS-5 (2019-2020), female sterilization accounted for 37.9% of all methods of family planning used in the country[1].Due to unforeseen circumstances like the death of a child or re-marriage, 1-3% of these women eventually seek for reversal of sterilization [2].Tubal anastomosis through a mini-laparotomy incision is a minimally invasive, cost-effective, and safe technique.

II. Materials and Methods

Sixteen women aged between 28-36 years (mean age 30.6 years), parity 1– 3, who requested reversal of tubal sterilization were included in the study. This study was conducted at Grant Government Medical College and Sir JJ Group of Hospitals, Mumbai in the year 2022.

Author σ: e-mail: aditijain95@gmail.com

Pre-operatively history was taken and the patients were thoroughly investigated. Detailed obstetric and gynecological history was taken, including details of the tubal sterilization procedure. Along with routine investigations for major operations, husband semen analysis was done in a few cases where the husband's age was more than 35 years. Detailed counseling of husband and wife was done regarding the procedure of recanalization and that the results will depend on many factors such as type of tubal ligation done, site of tubal ligation, condition of fimbria, length of the tube after anastomoses. They were also counseled regarding the complications after recanalization and the alternative option of in-vitro fertilization. Written valid informed consent was taken from all the patients. The surgery was performed post-menstrually.

Microsurgical tuboplasty was performed under spinal anesthesia. Cervical catheterization is done with foley's catheter no 8 and bulb inflated. A suprapubic transverse incision of 2-2.5 cm was taken. The principles of microsurgery were meticulously followed throughout. One side fallopian tube was traced with the help of Babcock's forceps and delivered outside the abdomen. The occluded segment of the tube was identified and resected till there was complete excision of pathological tissue. The medial and lateral edges were freshened and dilute methylene blue was pushed through intra-cervical foleys, staining the mucosa blue. No probes were used. Tissue planes were precisely aligned using an atraumatic technique by vicryl 6-0 (braided polyglactin) mounted on an atraumatic spatulated micro-point needle. The first suture was taken at 6 O'clock position in the mesosalpinx following which four sutures at 6', 3', 9', and 12 O clock were taken in the muscular layer and serosa to achieve end-to-end tubal anastomoses. The mucosa was avoided. Continuous irrigation with heparinized ringer lactate solution was done to visualize the operative field and prevent adhesions. Electrocoagulation with bipolar cautery was done to achieve hemostasis. Mopping was avoided. The tubal re-anastomoses was completed and chromopertubation was performed by injecting methylene blue dye from the cervical catheter to look for leakage of dye through the anastomosed site thereby confirm patency. 200 ml of Ringer lactate solution with 5000 IU heparin, 100 mg hydrocortisone, and 1500 IU hylase kept for hydro-flotation. The abdomen was closed in layers. On postoperative day 5, hydrotubation

with antibiotics, hylase, hydrocortisone, and heparin was done to promote healing and prevent adhesion formation. Patients were advised to use contraceptive measures for a period of 3 months to allow for the restoration of tubal condition after re-anastomosis.

III. Results

The mean age of study participants was 30.68 and majority were aged between 30-35 years.

Table 1: Age-wise distribution

Age	Number of patients (n)	Percentage %
< 30 years	6	37.5
30- 35 years	9	56.2
>35	1	6.2
Total	16	100%

The most common reason for tuboplasty was remarriage in our study that is 62.5% of the study population while death of more children was another reason that amounted to 37.5%.

Table 2: Reason for tuboplasty

Reason	Number of patients (n)	Percentage %
Death of one or more children	6	37.5
Remarriage	10	62.5
Total	16	100%

In our study included 16 women who requested for tubal recanalization, out of which one woman had a history of salpingectomy in view of ectopic pregnancy, therefore, a total of 31 tubes were operated upon. The site of anastomoses in these women are tabulated in table 3. The most common site was isthmic-ampullary.

Table 3: Site of anastomoses

Site of anastomoses	No. of tubes
Isthmic-ampullary	21
Isthmic-isthmic	6
Ampullary-ampullary	3
Cornual-isthmic	1

Tubal anastomosis through a mini-laparotomy incision was performed in sixteen patients, and the patency of each tube was assessed. The tubal length was more than 7cm in 27 tubes while the length of 4 tubes were less than 7cm.

Table 4: Fallopian tube length after tuboplasty and pregnancy outcome

Tube length	< 7 cm	>7cm	Total
No. of tubes	4	27	31
No. pregnancies	0	3	3

No patient experienced perioperative or postoperative complications. Patients were discharged from the hospital after a mean stay of 3 days in good general condition. Out of those who followed up, 3 women conceived. One woman conceived within 2 of months surgery in-spite of being advised contraception for 3 months post-operatively.

IV. Discussion

Tubal sterilization is currently the most accepted form of birth control in India. However, due to unforeseen events such as the death of a child or re-marriage, women eventually seek reversal. Estimating how many of these women would be candidates for reversal, if adequate facilities are available, is difficult. In our study, the women sought reversal for two reasons, the first being desire to have children with a new husband and the second being the death of the death of one or more children. Similar figures are also reported by others from our country [3], [4]. With the reversal of sterilization, there is an increased risk of ectopic pregnancy. Rates of 7 and 16% ectopic pregnancies after sterilization have been reported in some studies [5], [6]. However further follow up is required in our study to assess the risk of ectopic pregnancy.

Before undertaking tubal surgery for infertility, a thorough investigation of the couple is mandatory to exclude other factors which may be responsible for infertility. Pre-operative HSG was avoided as all patients had history of tubal ligation.

Garcia [7] reported the first microsurgical re-anastomosis of the fallopian tube, and the techniques of tubal microsurgery were advanced further by Winston [8]

and Gomel [9]. Consequently, the postoperative outcomes after microsurgical re-anastomosis have improved in comparison with those of macroscopic conventional reversal.

Principles of microsurgery such as use of fine non-inflammatory suture material, use of bipolar cautery, continuous irrigation, avoidance of contamination, minimum tissue damage, meticulous hemostasis and microsurgical instruments were used. As we could visualize the tube with naked eyes, we did not use any loupe or microscope, but one can always use them for magnification. We did not use any probe to identify the two cut ends as we believe they cause tubal mucosal damage. Instead, methylene blue dye was injected which stained the mucosa blue, thereby aiding in easy identification. Intra-operatively, we found that if the tube length is sufficient, re-anastomoses are done easily. Cornual ligation was slightly difficult for re-anastomosing due to lack of mobility. Although ligation was easy at the fimbrial end, functional results are awaited. In our study, 95% showed patency of tubes intra-operatively and 100% of tubes were patent in day 5 of hydrotubation.

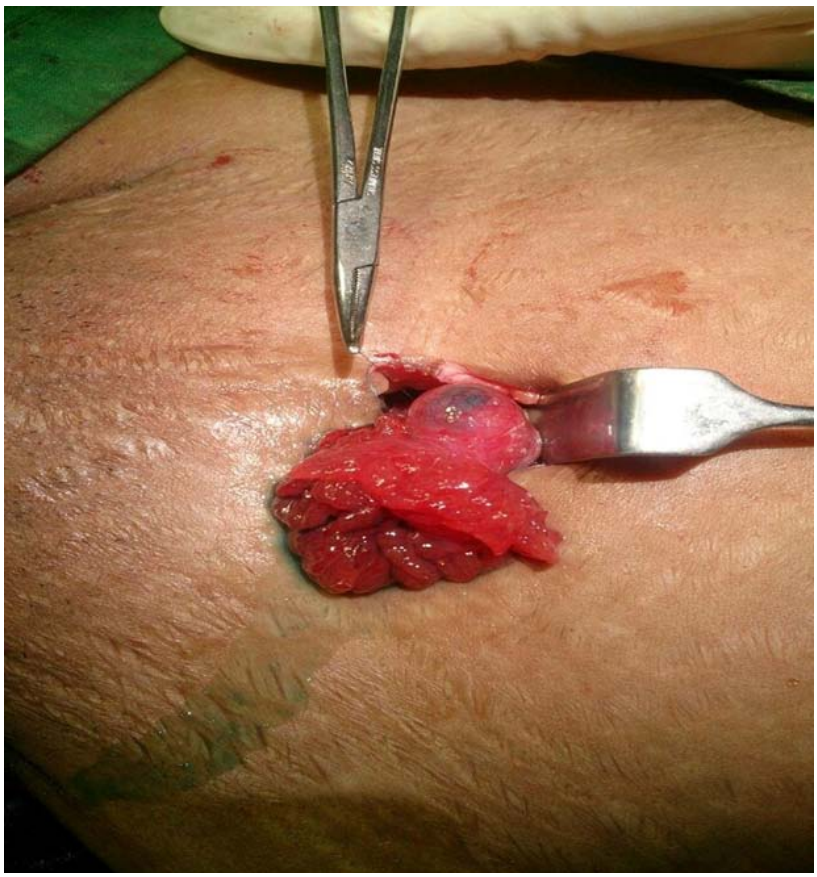


Figure 1: Patency of dye confirmed with methylene blue dye

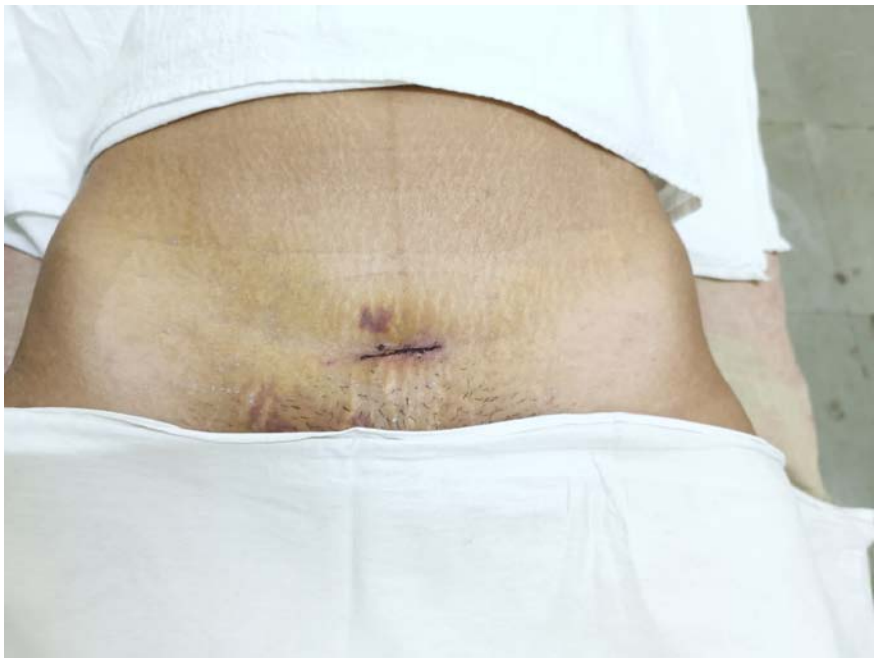


Figure 2: Incision line of microsurgical tuboplasty (2 to 2.5cm)

As compared to conventional laparotomy access, the mini-laparotomy technique is associated with decreased risk of tissue injury, foreign body contamination of the peritoneal cavity, adhesions, decreased post-operative pain and early rehabilitation. Later with the advancement of laparoscopy, laparoscopic tuboplasty started, although it is associated with minimal tissue injury, fewer adhesions and faster recovery, it requires longer operative time, risk of visceral injury and need for general anesthesia with expertise in the laparoscopic technique.

V. Conclusion

Mini-laparotomy tuboplasty done through a mini-laparotomy incision offers combined advantages of both conventional and laparoscopic recanalization. The surgeon must use an effective technique for the reversal of sterilization to minimize the failure rates and a method that causes minimal trauma and aim at preserving the length of the tube so that reversal is more likely to be successful. Tubal bypass through in-vitro fertilization is a costly affair that not all can afford, hence the need for tuboplasty is rising. Therefore one can definitely try and master tuboplasty through a mini-laparotomy incision.

References Références Referencias

1. International Institute for Population Sciences (IIPS) and ICF. 2021. National Family Health Survey (NFHS-5), India, 2019-21: Mumbai: IIPS.
2. Grunert GM, Drake TS, Takaki NK. Microsurgical re-anastomosis of the fallopian tubes for reversal of sterilization. Obstetrics and Gynecology. 1981 Aug 1; 58(2): 148-51.
3. Brar MK, Kaur J, Kaur S. A study of microsurgical re-anastomosis of the fallopian tubes for reversal of sterilization. J ObstetGynaecol India. 2000; 6:75-.
4. Henry A, Rinehart W, Piotrow PT. Reversing female sterilization. Population reports (Washington, DC). Series C, Female sterilization. 1980 Sep (8): C97-123.
5. Chi IC, Gardner SD, Laufe LE. The history of pregnancies that occur following female sterilization. International Journal of Gynecology & Obstetrics. 1979 May; 17(3): 265-7.
6. Wallach E, Tatum HJ, Schmidt FH. Contraceptive and sterilization practices and extrauterine pregnancy: a realistic perspective. Fertility and sterility. 1977 Apr 1; 28(4): 407-21.
7. Garcia CR. Oviductal anastomosis procedures. Human sterilization. 1972:116.
8. Winston RM. Microsurgical reanastomosis of the rabbit oviduct and its functional and pathological sequelae. BJOG: An International Journal of Obstetrics & Gynaecology. 1975 Jul; 82(7): 513-22.
9. Gomel V. Tubal reanastomosis by microsurgery. Fertility and Sterility. 1977 Jan 1; 28(1): 59-65.

Global Journal of Medical Research: E
Gynecology and Obstetrics
Volume 23 Issue 1 Version 1.0 Year 2023
Type: Double Blind Peer Reviewed International Research Journal
Publisher: Global Journals
Online ISSN: 2249-4618 & Print ISSN: 0975-5888

A Cross-Sectional Study on Prediction of Preterm Delivery with Phosphorylated Insulin like Growth Factor Binding Protein-1 Test

By Dr. Sana Tak, Dr. Pushpa Nagar, Dr. Akansha Kumawat, Dr. Aditi Bansal & Dr. Bhavini

Abstract- *Aim and objective:* To predict preterm deliveries in symptomatic patients using a bedside kit for phosphorylated Insulin like Growth Factor Binding Protein-1 in cervical secretion. It will enrich obstetricians in early identification, preparedness and timely obstetricians' interventions to reduce anticipated fetal complications in threatened preterm.

Materials and methods: It was hospital based cross-sectional study including 78 pregnant women between 28 weeks to 37 weeks of gestation with threatened preterm labor. Phosphorylated Insulin Like Growth Factor Binding Protein Test was done and data analysis was done using Student's t – test , Receiver operator characteristic curve and chi square test.

Keywords: *preterm labor, phIGFBP-1.*

GJMR-E Classification: *DDC Code: 615.365 LCC Code: QP572.I5*

Strictly as per the compliance and regulations of:

A Cross-Sectional Study on Prediction of Preterm Delivery with Phosphorylated Insulin like Growth Factor Binding Protein-1 Test

Dr. Sana Tak [α], Dr. Pushpa Nagar [σ], Dr. Akansha Kumawat [ρ], Dr. Aditi Bansal [ω] & Dr. Bhavini [¥]

Abstract- Aim and objective: To predict preterm deliveries in symptomatic patients using a bedside kit for phosphorylated Insulin like Growth Factor Binding Protein-1 in cervical secretion. It will enrich obstetricians in early identification, preparedness and timely obstetricians' interventions to reduce anticipated fetal complications in threatened preterm.

Materials and methods: It was hospital based cross-sectional study including 78 pregnant women between 28 weeks to 37 weeks of gestation with threatened preterm labor. Phosphorylated Insulin Like Growth Factor Binding Protein Test was done and data analysis was done using Student's t – test, Receiver operator characteristic curve and chi square test.

Results: Among 78 women with threatened preterm labor, 53(67.9%) tested positive for phIGF-BP1 out of which 52(98.1%) delivered preterm and among them 36(67.9%) delivered within 48hours of the test. So the test was extremely sensitive in predicting preterm labor.

Conclusion: phIGFBP-1 test had a great role in the management of women presented with threatened preterm labor . It will allow more focussed management of female and avoid un-necessary admissions and treatment , to contain health care costs.

Keywords: preterm labor, phIGFBP-1.

I. Introduction

Preterm labor refers to the onset of labor after fetal viability but before 37 completed weeks of gestation. The diagnostic criteria are onset of increasingly frequent and painful uterine contractions (atleast 4 contractions per 20 minutes) with progressive effacement and dilatation of the cervix i.e., 80% cervical effacement and atleast 2cm dilatation (or cervical length <1cm).[1]

It is a major challenge in perinatal health care. Preterm birth occurs in 5% to 18% of all deliveries worldwide. It is estimated that 15 million preterm births occur each year with 1.1 million infants dying from preterm birth complications.[1]

Author α ρ ¥: Resident doctor, Department of Obstetrics and Gynaecology, SMS Medical College, Jaipur.
e-mail: sanatak805@gmail.com
Author σ: Senior professor, Department of Obstetrics and Gynaecology, SMS Medical College, Jaipur .
Author ω: Associate professor, Department of Obstetrics and Gynaecology, SMS Medical College, Jaipur.

Prediction of preterm labor enables taking early action for preterm birth as in- utero transfer to tertiary care centres, reasonable administration of corticosteroids while avoiding un-necessary use, magnesium sulphate treatment for neuroprotective effect and antibiotic treatment in case of infection.[2]

Current screening tests for the prediction of preterm labor can be divided into three general categories :-

1) Risk factor assessment
2) Cervical measurement
3) Bio-chemical markers

One of the early changes that precede preterm birth is cervical shortening, which may be detected even several weeks prior to the onset of active labor. But due to limitations in ultrasound availability and operator expertise, cervical length alone cannot be reliably utilised to predict preterm labor or used as routine screening tool.[3]

Cervico-vaginal fluid, a complex mixture of secretions from vagina, endocervix, endometrial decidua and amniochorion serves as an important diagnostic tool for preterm labor prediction .Two most commonly used biochemical markers used for prediction of preterm labor are -fetal fibronectin and phosphorylated Insulin like growth factor binding protein -1(ph-IGFBP-1).

Fetal fibronectin is a glycoprotein produced by amniocytes and cytotrophoblasts .It is normally found in cervico-vaginal fluid before 22 weeks of gestation but its presence between 24 to 34 weeks of gestation indicates a risk of preterm birth. But this test has several disadvantages or limitations including high cost, limited availability, sexual intercourse or vaginal examination interferes with the test and reduces its accuracy

Phosphorylated Insulin like growth factor binding protein -1 (ph-IGFBP-1) was requested as a marker for predicting preterm birth for being positive at significantly higher rates in cervical fluids of patients with preterm birth. An immune chromatographic test(one step dipstick test) detects ph-IGFBP-1 in cervix, can be used from 22 weeks onwards with fast results. Test results are not affected by urine, intercourse semen, vaginal medications, lubricants or infections .It has 98%

(high) negative predictive value that helps to avoid unnecessary treatment and reduces cost.[4]

II. Aim and Objectives

To predict preterm deliveries in symptomatic patients.

To assess sensitivity, specificity, positive predictive value and negative predictive value of the phosphorylated Insulin like Growth Factor Binding Protein-1 test for prediction of preterm labour in symptomatic patients.

III. Materials and Methods

The study was conducted in the Department of Obstetrics and Gynaecology, SMS Medical College, Jaipur. Women with singleton pregnancy 28 to 37 weeks of gestation with intact fetal membranes, who presented with threatened preterm labour were included in the study after taking written informed consent. Pregnant women with Preterm premature rupture of membranes (PPROM), advanced preterm labour, those women who require iatrogenic preterm induction of labor were excluded.

The study sample was 78 cases and they were subjected to detailed history if any were noted. Abdominal examination was done for presentation of fetus and frequency of uterine contractions. Amniotic fluid leak was confirmed on per speculum examination and the test for detection of phosphorylated Insulin like Growth Factor Binding Protein-1 was done. The test was positive if two blue lines appeared and negative if only one blue line was seen.

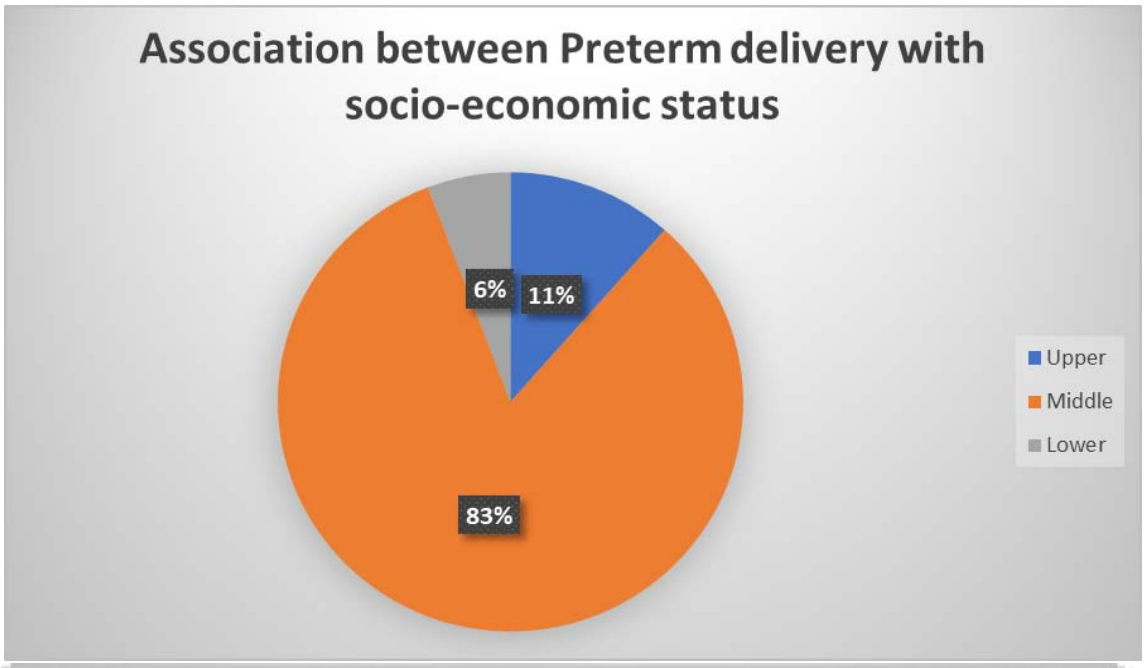
IV. Statistical Analysis

The data collected was entered in MS excel sheet. Continuous variables were summarized as mean and were analyzed by using unpaired t test. Nominal / categorical variables were summarized as proportions and were analyzed by using chi-square/Fischer exact test. Pvalue <0.05 was taken as significant. Diagnostic accuracy was assessed using following terms: Sensitivity, Specificity, PPV and NPV. Medcalc 16.4 version software was used for all statistical calculations.

V. Results

Table 1: Socio-demographic factors

Variable	Preterm delivery		p-value
	Yes	No	
Age			< 0.143
18-25years	33(63.5%)	12(46.2%)	
26-30years	17(32.7%)	10(38.5%)	
>30years	2(8.8%)	4(15.4%)	
Socio-economic status			<0.223
Upper	6(11.5%)	2(7.7%)	
Middle	43(82.7%)	19(73.1%)	
Lower	3(5.8%)	5(19.2%)	
Residence			<0.150
Urban	29(55.8%)	10(38.5%)	
Rural	23(44.2%)	16(61.5%)	
BMI			<0.709
<18.5kg/m2	12(63.2%)	7(36.8%)	
18.5-22.9kg/m2	40(67.8%)	19(32.2%)	



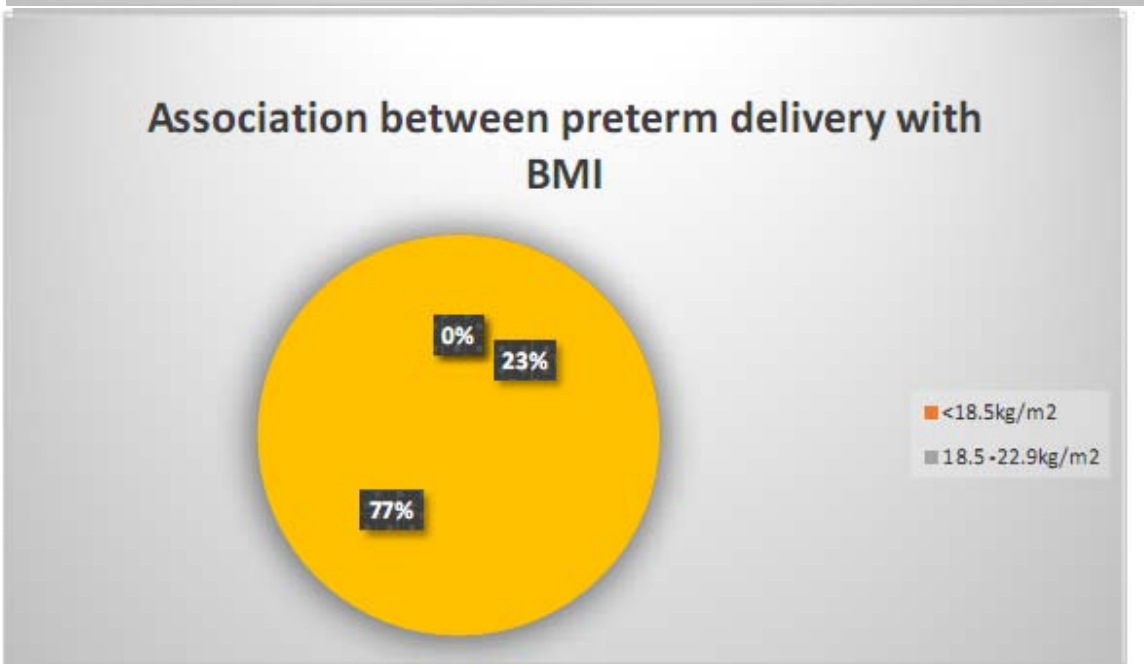


Table 2: Risk factors for preterm delivery

Risk factor	Preterm delivery	
	Yes	No
History of vaginosis (31)	24(77.4%)	7(22.6%)
History of threatened abortion (33)	24(72.7%)	9(27.3%)

p-value (history of vaginosis)- <0.0102

p-value (history of threatened abortion)-<0.331

Table 3: Complication in last delivery

Complication in last delivery	Preterm delivery	
	Yes	No
Preterm delivery(58)	35(60.34%)	23(39.66%)
Vaginal infection (12)	9(75%)	3(25%)
UTI(5)	5 (100%)	0(0.00%)

p-value-<0.200

Table 4: Association between preterm birth and ph-IGFBP-1 test

Preterm delivery	PhIGFBP-1 test	
	Positive	Negative
Yes(52)	52 (100%)	0(0.00%)
No(26)	1(3.85%)	25(96.15%)

p-value-<0.001

Table 5: Association between phIGF BP-1 test and test delivery interval

Test delivery interval	PhIGFBP-1 test	
	Positive	Negative
<=48hours(36)	36(100%)	0(0.00%)
48hours but within 7days (9)	9(100%)	0(0.00%)
>7 days (33)	8(24.24%)	25(75.76%)

p-value-<0.001

VI. Results and Discussion

An accurate diagnosis of preterm labor is clinically difficult. In this study, we evaluated the value of the rapid phIGFBP-1 test in predicting preterm births in patients. In the study, majority of the participants (78) belonged to age group 18-25 years (45) and among this group, around 63.5% (33) had preterm delivery. Naoko Kozuki et al(2013)[5] reported in their study that early and late maternal age is an important risk factor for preterm labor. In this study, participant distribution is equal (50%) among rural and urban areas. Various studies have given variable results on association of preterm delivery with ethnicity but data on distribution in areas are non-conclusive.

In this study, 10.3% (8) women were from upper economic class, 79.5% (62) from middle economic class and 10.3% (8) were from lower socio-economic class. Among them maximum preterm delivery around 82.7% (43) were in middle socio-economic group. This finding was not in accordance with the study done by L. Ochoe (2021)[6]where poor or lower socio-economic status with lower education and income levels had more chances of preterm delivery.

In this study, 75.6% (59) women had BMI between 18.5 -22.9 kg/m2 and among them 67.8% (40) had preterm delivery. The exact mechanisms explaining the link between BMI and preterm delivery are not well known, however one theory suggests that significant preterm delivery risk increasing continuously with rising BMI.

In our study, among participants (78) around 66.7% (52) delivered preterm. Among preterm delivered 77.4% (24) had a history of vaginosis and 72.7% (24) had a history of threatened abortion in the present pregnancy. As per Kurki et al(1992)[7], Bacterial vaginosis had 2- 6 times increased risk for preterm labor.

As per the study by Salah Roshdy (2012)[8], women with threatened abortion had a significantly increased risk of preterm labor. In our present study, those who delivered preterm, 71.4% (35) had a history of previous preterm delivery, 18.4% (9) had a history of vaginal infection in previous delivery and 10.2% (5) had a history of UTI in previous pregnancy. As per the study by Yang (2017), a prior preterm birth increases the risk for a subsequent preterm birth with higher odds.

In our study, out of 78 women, 53 (67.9%) tested positive for phIGFBP-1 test and 25 (32.1%) tested negative result. Those who tested positive 52 (98.1%) delivered preterm and only 1 (1.9%) delivered term. Those who tested negative were not delivered preterm.

As the test has a high negative predictive value, this may enable physicians to prevent overtreatment of patients with preterm labor. Therefore, many unwanted side effects and complications of potentially hazardous tocolytic therapy can be prevented.

In our study those who tested positive 67.9%(36) for phIGFBP-1(53) were maximally delivered within 48hours and 17% (9) delivered between 48 hours to 7 days and 15% (8) delivered after 7days of the test. Those who tested negative (25) were all delivered after 7 days of the test. So the test was extremely sensitive in predicting preterm labor.

VII. Limitation of the Study

The sample size of study may be small for the result to be significant enough to be applicable to the general population, but it is big enough to be significant for the study population.

VIII. Conclusion

In this study, results show that there is a role of cervical phIGFBP-1 test in the management of women presenting with suspected preterm labor, it may replace cervical ultrasonography and fetal fibronectin in the future or atleast serve as a useful adjunct to these tests. Thus, it will allow more focused management of women who are more likely to deliver preterm and perhaps avoid unnecessary admissions and treatment, to curtail health care costs.

Conflicts of interest: No potential conflicts of interest were reported by the authors.

Informed consent statement: All subjects here were already informed and gave consent.

Provenance and peer review: Not commissioned, externally peer-reviewed.

Declaration of competing interest: None.

Acknowledgement

The authors would like to thank everyone who supported and assisted throughout all aspects of our study and for their help in writing the manuscript.

References Références Referencias

1. Pallavi S. Vishwekar, Anahita R. Chauhan, NajuTurakhia, International Journal Of Reproduction, Contraception, Obstetrics And Gynecology, Vol 6, No 8 ,2017- Prediction of preterm delivery with a novel bedside test.
2. Koullali B et al (2016) Risk assessment and management to prevent preterm birth.
3. WHO-Preterm birth 2016 [updated November 201624/3/2017].
4. Jung E et al (2016) -Prediction of impending preterm delivery based on sonographic cervical length and different cytokine levels in cervicovaginal fluid in preterm labor.
5. Naoko Kozuki, Arme CC Lee (2013) - The Association of parity and maternal age with small for gestational age, preterm and neonatal and infant mortality.
6. L.ochoa-Association of neighbourhood socio-economic trajectories with preterm birth and small-for-gestational-age in the Netherlands: a nationwide population based study.
7. Kurki, Tapio MD (1992). Bacterial vaginosis in preterm labour.
8. Pregnancy Outcome in Women with Threatened Miscarriage-(2012) a Year Study-Salah Roshdy Ahmed, Mohamed El-Khatem El-Samman.

This page is intentionally left blank

Global Journal of Medical Research: E
Gynecology and Obstetrics
Volume 23 Issue 1 Version 1.0 Year 2023
Type: Double Blind Peer Reviewed International Research Journal
Publisher: Global Journals
Online ISSN: 2249-4618 & Print ISSN: 0975-5888

Uniting the Uteri: A Case Series

By Dr. Ashok R. Anand, Dr. Adithi Jayaprakash, Dr. Pushpa C. & Dr. Aditi R. Jain

Abstract- *Background:* Metroplasty is a reconstructive surgery to repair congenital anomalies of the uterus. Anomalous uteri are known to cause infertility and recurrent abortions due to defective implantation, restrictive foetal growth and malpresentations.

Aim: To discuss our experiences and surgical techniques with various cases of metroplasty, in women with structural uterine anomalies with infertility or recurrent abortions at a tertiary care hospital in Mumbai.

Case description: A descriptive study of case series of metroplasty conducted in a tertiary care hospital in women with bicornuate and didelphys uterus by opening the uterine cavities by incision on the medial aspect of the hemicolpos and approximating the myometrial edges and suturing them to create a single uterine cavity.

Keywords: *metroplasty, mullerian anomalies, vaginoplasty, bicornuate uterus, uterine didelphys, recurrent pregnancy loss.*

GJMR-E Classification: *NLMC Code: WI480*

Strictly as per the compliance and regulations of:

Uniting the Uteri: A Case Series

Uniting the Uteri: A Case Series on Metroplasty in Mullerian Anomalies

Dr. Ashok R. Anand [α], Dr. Adithi Jayaprakash [σ], Dr. Pushpa C. [ρ] & Dr. Aditi R. Jain [ω]

Abstract- ***Background:*** Metroplasty is a reconstructive surgery to repair congenital anomalies of the uterus. Anomalous uteri are known to cause infertility and recurrent abortions due to defective implantation, restrictive foetal growth and malpresentations.

Aim: To discuss our experiences and surgical techniques with various cases of metroplasty, in women with structural uterine anomalies with infertility or recurrent abortions at a tertiary care hospital in Mumbai.

Case description: A descriptive study of case series of metroplasty conducted in a tertiary care hospital in women with bicornuate and didelphys uterus by opening the uterine cavities by incision on the medial aspect of the hemicolpos and approximating the myometrial edges and suturing them to create a single uterine cavity.

Conclusion: By unification of two smaller uterine cavities, metroplasty restores a normal anatomy of the uterine cavity as is required for positive implantation and good obstetric outcomes.

Clinical Significance: After metroplasty, chances of conception and probability of carrying conception to full term rises significantly.

Keywords: metroplasty, mullerian anomalies, vaginoplasty, bicornuate uterus, uterine didelphys, recurrent pregnancy loss.

I. Background

Metroplasty, first illustrated in 1907 by Strassman, is a reconstructive surgery used to repair congenital anomalies of the uterus including septate, bicornuate and didelphys uterus. This surgery involves removal of the abnormal tissue that separates the uterine cornua, and then creating a normal shaped uterus by suturing in multiple layers.[1]

Although most women with Mullerian anomalies can conceive without difficulty, obstetric complications and adverse pregnancy outcomes have been more commonly reported in anomalous uteri. They are associated with a high rate of recurrent spontaneous abortions, preterm labour, cervical incompetence, malpresentations, foetal growth restriction, high risk of uterine rupture, retained placenta and post-partum haemorrhage. Risk of pregnancy wastage differ with the type of uterine anomaly— maximally in bicornuate and septate uterus, i.e., 60%, 55% in uni-cornuate and didelphys uteri and 35% in arcuate uterus.[2] Uterine anomalies are seen in approximately 12.6% (1.8-37.6%) of patients with recurrent pregnancy loss as compared with 4.3% (2.7-16.7%) of the general population.[2] Often, they are seen accompanying various renal anomalies. According to Thompson and Lynn,[3] 40% of females with congenital absence of the kidney are found to have associated genital anomalies.

Surgical interventions are indicated when there is obstruction causing associated pelvic pain and endometriosis and for women with poor obstetric outcomes.[4] Before metroplasty, extra-uterine causes need to be ruled out. The goals of metroplasty are restoration of pelvic anatomy, preservation of fertility, and treatment of pelvic pain and endometriosis.

We hereby discuss 5 cases of congenitally anomalous uteri, in whom we performed metroplasty.

II. Case Description

The procedure was initiated by a transverse incision in the lower abdomen through which the abdomen was opened and uterus was visualised. To minimise the blood loss, injection vasopressin was injected into the myometrium or temporary bilateral uterine artery ligation was done using a constricting Foley's catheter. In cases of bicornuate and didelphys uteri, both the cornua are deeply incised on the median side in their long axis to expose both the uterine cavities. Care was taken to avoid injury to the fallopian tubes. The cut edges of the myometrium were then approximated and sutured vertically anteriorly and posteriorly with Vicryl 2-0 in continuous manner in three layers in order to create a single uterine cavity.

Case 1: OHVIRA / Herlyn-Werner-Wunderlich Syndrome: Uterine didelphys + Hematometra/ Hematocolpos + Absent Right Kidney

A 28-year-old female, married for 10 years, presented with Primary infertility. Pelvic examination showed *unicollis* and presence of *bogginess* in the right lateral fornix.

USG showed absence of right kidney and two separate uterine cavities and cervices- s/o **Uterine didelphys.** ESHRE Classification **U3BC2**, with approximately equally sized right and left horns. A collection of ~5cc was seen in right cervical canal and upper third of vagina s/o **Hematometra + Hematocolpos.**

Author α: Prof. & HOD, Grant Government Medical College and Sir J. J. Group of Hospitals, Mumbai, India.
e-mail: ashokanand1616@gmail.com
Author σ ρ ω: Resident, Grant Government Medical College and Sir J. J. Group of Hospitals, Mumbai, India.

The two uterine horns were united by metroplasty, and follow-up USG showed a single uterine cavity with resolution of hematometra and hematocolpos. (Fig. 1)

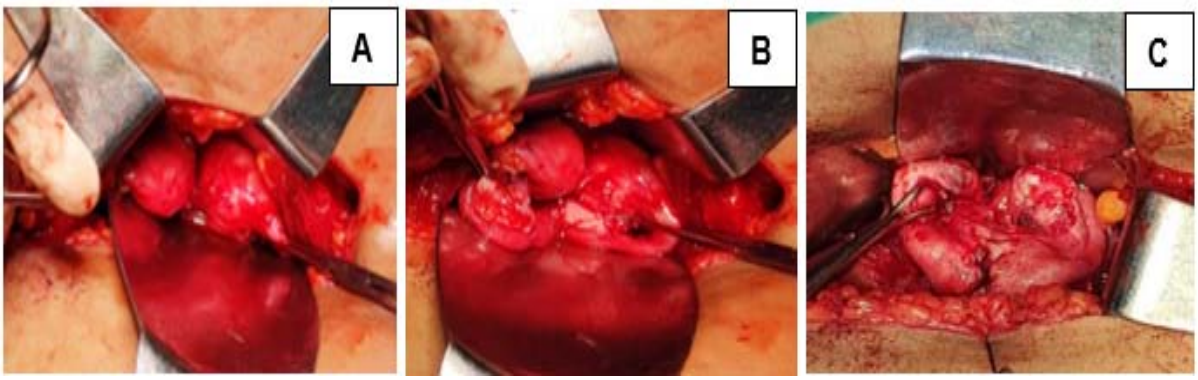


Figure 1: A: Uterine didelphys. B: Cavity opened. C: Edges of cavity approximated and sutured.

Case 2: Bicornuate Uterus

A 33-year-old female, married for 9 years, with previous 2 spontaneous abortions at 4-5 months of gestation, presented with secondary infertility. USG and HSG revealed bicornuate uterus with approximately equal sized right and left horns. Metroplasty was performed and follow-up USG showed a single uterine cavity. (Fig. 2)

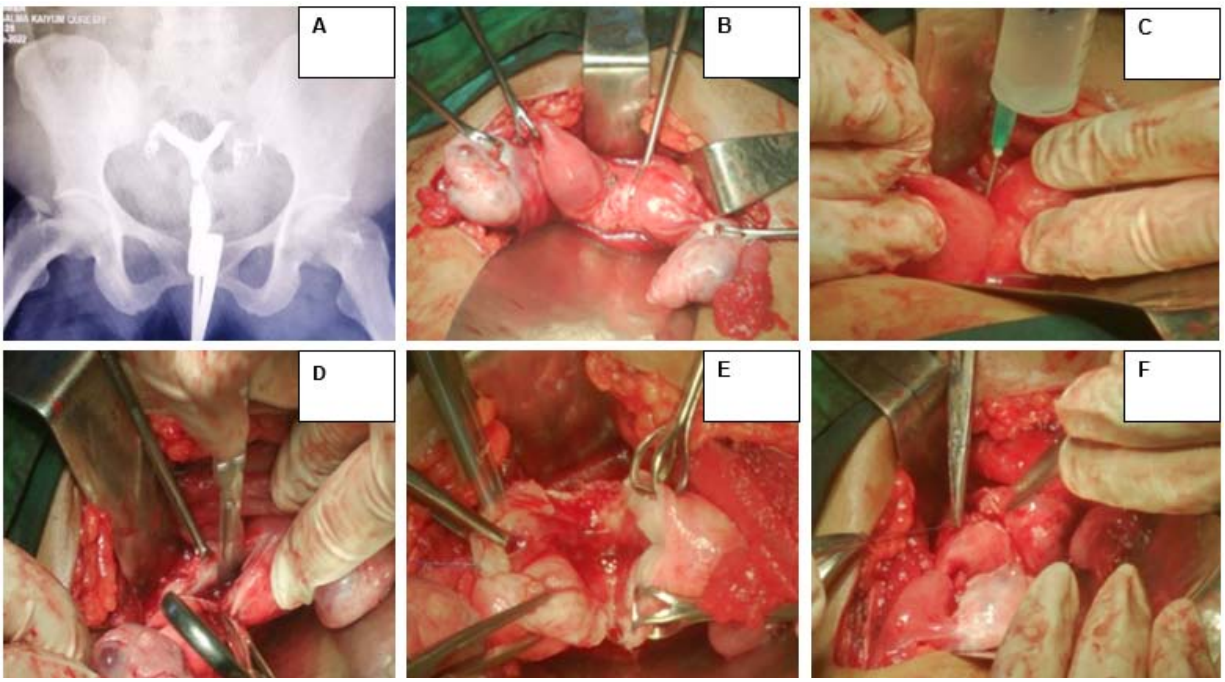


Figure 2: A: HSG s/o Bicornuate uterus. B: Bicornuate uterus on laparotomy. C: Vasopressin injected to minimize the blood loss during surgery. D: Transverse incision taken over uterine fundus. E: Uterine cavity opened. F: Edges approximated & sutured vertically

Case 3: Bicornuate Uterus

A 35-year-old, female married for 8 years, with a spontaneous abortion at 4th month of gestation, presented with Secondary infertility. USG showed bicornuate uterus with almost equal right and left horns, communicating in the lower third of the uterus, s/o Bicornuate uterus. ESHRE Class: U3a. HSG confirmed the same. Follow up- HSG post metroplasty showed resolution with slight depression in the fundal region. (Fig. 3)

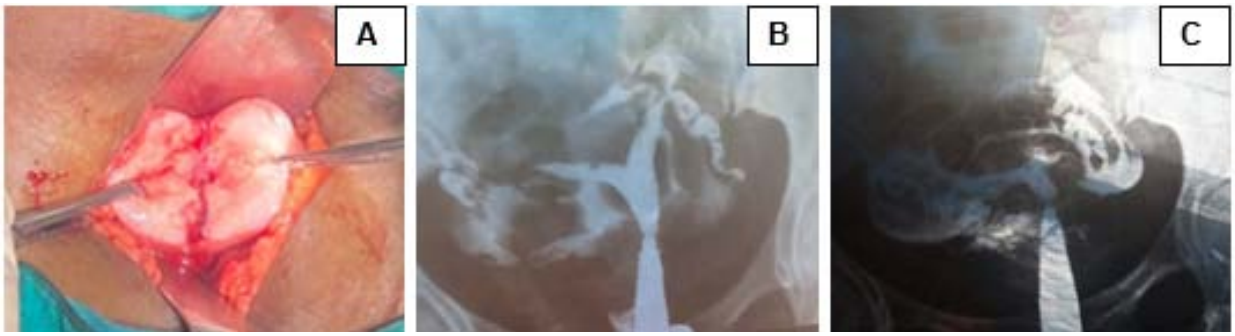


Figure 3: A: Opening the uterine cavity for metroplasty.

B and C: Comparison of pre-op and post-op HSG

Case 4: Bicornuate Uterus

A 34-year-old female married for 9 years, with 4 spontaneous abortions at 3-4 months of gestation, presented with secondary infertility. USG showed Bicornuate uterus with almost equal right and left horns, communicating in the lower third of the uterus, s/o Bicornuate uterus, with HSG confirming the diagnosis. Post metroplasty, she had a successful pregnancy till term and underwent LSCS uneventfully. (Fig. 4)

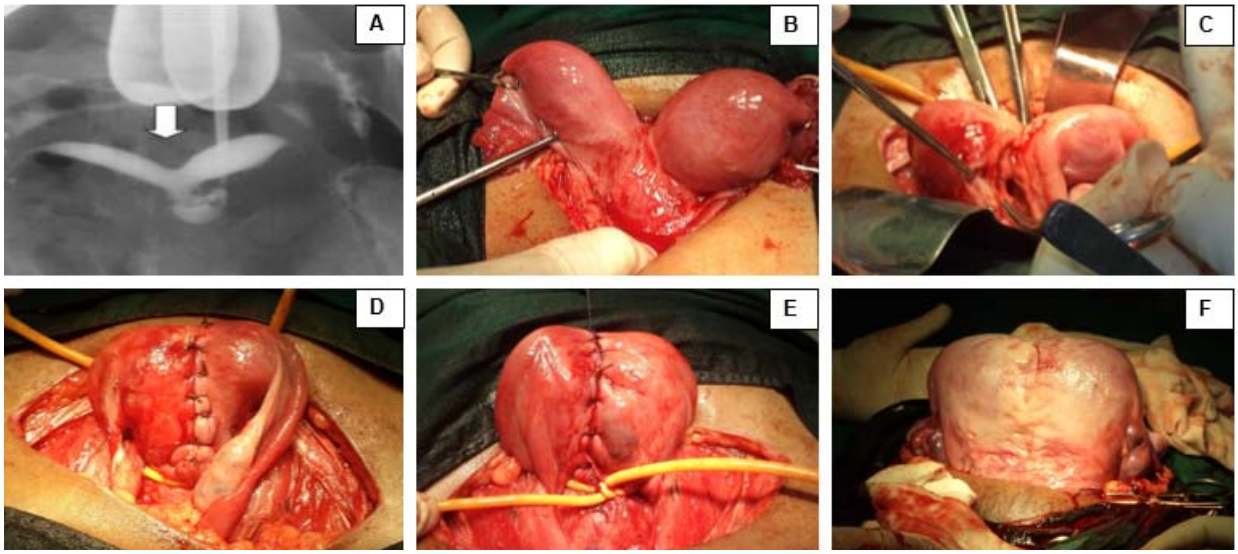


Figure 4: A: HSG s/o Bicornuate uterus. B: Bicornuate uterus. C: Temporary ligation with Foleys and opening uterine cavity. D and E: Anterior and posterior surface after suturing. F: Healed uterus as seen during Caesarean section.

Case 5: Uterine didelphys with high vaginal septum

A 29-year-old, female married for 2 years, nulligravida, presented with dyspareunia and primary infertility. Patient was a known case of uterine didelphys with vertical vaginal septum and gives history of being operated for imperforated anus in childhood. Pelvic examination showed complete vertical vaginal septum with two vaginal canal leading to two separate cervices. Both the cervices were short and flushed with vagina and UCL was measured as 3 inches on both sides. USG showed uterine didelphys with vertical vaginal septum. Patient underwent vaginoplasty and metroplasty and post operatively, dilatation with Hegars No. 28 dilators was advised. The patient was able to have normal sexual function. (Fig. 5)

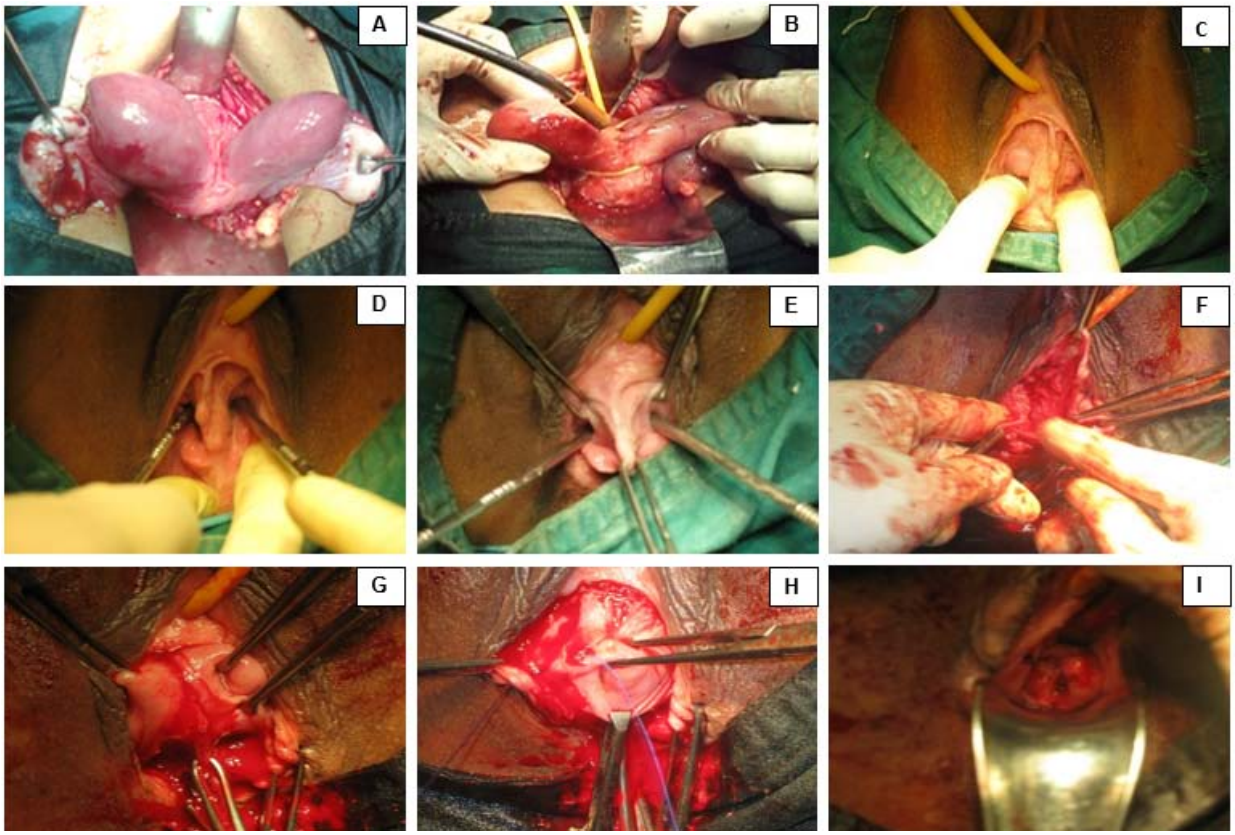


Figure 5: A: Uterine didelphys. B: Opening cavity during metroplasty. C: Complete vertical septum infiltrated with saline. D: Vaginal canals opening into two separate cervical openings. E: Anterior lip of cervices held with Allis' forceps and vertical incision taken over septum. F: Plane of dissection maintained along the septum. G: Redundant mucosa cut. H: Cut ends sutured with vagina with Vicryl 3-0. I: Vagina with two cervices.

Post procedure, the patients were advised to avoid conception for at least 1 to 2 years and all future pregnancies are to be terminated by Caesarean section to avoid risk of uterine rupture at the relatively weak suture sites during labour.

All women were advised a repeat HSG and USG after 3 months, which in all the cases confirmed the unison of the uteri into a single cavity.

III. Discussion and Clinical Significance

Surgery is not a rule for all cases of uterine anomalies. Most women with minor uterine anomalies conceive spontaneously and carry pregnancy till term. However, metroplasty is indicated when there is history of two or more fetal wastages, and when other causes are ruled out.

A review of literature reveals that Strassman metroplasty significantly improves the obstetric outcomes in women with Mullerian anomalies. The rate of fetal wastage prior to metroplasty was found to range from 70-88% in various studies, in comparison to live birth rates of 81-85% after metroplasty.[5-11]

Prior to abdominal metroplasty, the uterine anomaly needs to be confirmed. Accuracy of hysterosalpingogram alone is only 55% for differentiation of septate uterus from the bicornuate uterus[13], and hence is confirmed by 3-D USG and MRI. A more suitable modality in settings where facilities are available, hystero-laparoscopy can be performed, wherein septate uterus, when detected can be corrected by hysteroscopic resection in the same setting, with minimal invasion, thus avoiding unnecessary laparotomies. However, the enlarging use of hysteroscopic metroplasty is not wholesome as it may create cervical fragilization, thus necessitating a cervical cerclage in order to prevent 2nd trimester pregnancy loss. The abdominal metroplasty still remains the operation of choice destined to treat cases of bicornuate uterus or uterus didelphys due to high risk of perforation during hysteroscopic correction.

References Références Referencias

1. Hoffman BL, et al. Williams Gynecology. 3rd Ed. 2016; 422.
2. G. F. Grimbizis, M. Camus, B. C. Tarlatzis, J. N. Bontis, and P. Devroey. Clinical implications of uterine malformations and hysteroscopic treatment results. Human Reproduction Update. 2001; 7: 161-174.

3. Thompson DP, Lynn HB. Genital anomalies associated with solitary kidney. Mayo Clin Proc. 1966; 41: 538.
4. Rackow, B. W., & Arici, A. Reproductive performance of women with müllerian anomalies. Current opinion in obstetrics & gynecology. 2007; 19: 229-237.
5. Homer, Hayden Anthony. Modern management of recurrent miscarriage. Australian and New Zealand Journal do Obstetrics and Gynaecology. 2018; 59: 36-44.
6. Strassman EO. Fertility and unification of double uterus. FertilSteril. 1966; 17: 165-76.
7. Papp Z, Mezei G, Gávai M, Hupuczi P, Urbancsek J. Reproductive performance after transabdominal metroplasty: a review of 157 consecutive cases. J Reprod Med. 2006; 51: 544-52.
8. R. Tomasz, M. Marta, and B. Aleksandra. Clinical effectiveness of Strassman operation in the treatment of bicornuate uterus. Ginekologia Polska. 2009; 8: 88-92.
9. F., Valle R. Hysteroscopic treatment of partial and complete uterine septum. International journal of fertility and menopausal studies. 1996; 41: 310-315.
10. Lolis DE, Paschopoulos M, Makrydimas G, et al. Reproductive outcome after Strassman metroplasty in women with a bicornuate uterus. J Reprod Med. 2005; 50: 297-301.
11. Tomasz R, Marta M, Aleksandra B. Clinical effectiveness of Strassman operation in the treatment of bicornuate uterus. Ginekol Pol. 2009; 2: 88-92.
12. Juillion, Perrine. What is the difference between bicornuate and didelphys uterus? Available at: https://studybuff.com/what-is-the-difference-between-bicornuate-and-didelphys-uterus/

This page is intentionally left blank

Global Journal of Medical Research: E
Gynecology and Obstetrics
Volume 23 Issue 1 Version 1.0 Year 2023
Type: Double Blind Peer Reviewed International Research Journal
Publisher: Global Journals
Online ISSN: 2249-4618 & Print ISSN: 0975-5888

Levonorgestrel Releasing Intrauterine System versus Dienogest for Symptomatic Adenomyosis

By Prof. Jesmine Banu & Sharmin Sultana

Abstract- *Introduction:* Adenomyosis is a common, estrogen-dependent, a benign gynaecological disease characterized by endometrial glands and stroma invading, implanting, and proliferating within the myometrium to form diffuse or localized lesions. Adenomyosis is common in women of childbearing age. The signs and symptoms include dysmenorrhea, menorrhagia, abnormal uterine bleeding, enlarged uterus, dyspareunia, and infertility, which can seriously affect the patient's quality of life. The prevalence of adenomyosis varies widely from 5% to 70%, depending on the method used for diagnosis and the rate of diagnosis during hysterectomy is approximately 20– 30%.

Aim of the study: The aim of this study was to evaluate and compare the effectiveness between LNG-IUS and Dienogest among the woman with symptomatic adenomyosis.

Keywords: *adenomyosis, dysmenorrhoea, LNG-IUS, dienogest.*

GJMR-E Classification: *NLMC Code: WP 660*

Strictly as per the compliance and regulations of:

Levonorgestrel Releasing Intrauterine System versus Dienogest for Symptomatic Adenomyosis

Prof. Jesmine Banu [α] & Sharmin Sultana [σ]

Abstract- *Introduction:* Adenomyosis is a common, estrogen-dependent, a benign gynaecological disease characterized by endometrial glands and stroma invading, implanting, and proliferating within the myometrium to form diffuse or localized lesions. Adenomyosis is common in women of childbearing age. The signs and symptoms include dysmenorrhea, menorrhagia, abnormal uterine bleeding, enlarged uterus, dyspareunia, and infertility, which can seriously affect the patient's quality of life. The prevalence of adenomyosis varies widely from 5% to 70%, depending on the method used for diagnosis and the rate of diagnosis during hysterectomy is approximately 20– 30%.

Aim of the study: The aim of this study was to evaluate and compare the effectiveness between LNG-IUS and Dienogest among the woman with symptomatic adenomyosis.

Methods: This was a randomized control clinical trial and was conducted in the Department of Reproductive Endocrinology and Infertility, Bangabandhu Sheikh Mujib Medical University (BSMMU), Shahbag, Dhaka, Bangladesh during the period from ---------- to ----------. We included 20 patients with symptomatic adenomyosis diagnosis confirmed by transvaginal ultrasound in this study. All patients were divided by sequentially numbered sealed opaque envelops into two groups- Group A (who received LNG-IUS)& Group B(who received dienogest). Among of 20 patients, 10 were in each group.

Result: In total 20 patients from both the groups completed the study. In our study we found that majority of our patients (75%) were aged between 25 to 34 years old and 25 % were aged between 35 to 45 years old. We found the Mean ± SD of age was 34.80 ± 3.79 & 28.60 ± 3.17 and BMI was 28.07± 2.72 & 26.06 ± 2.46 respectively in group A & B. At 3rd month the mean of VAS was 1.10 ±1.10 & 4.30± 2.41; hemoglobin level was 11.57 ±1.33 & 11.09± 0.53 and uterine volume was 210.10 ±105.49 & 202.77 ± 118.33 among group A & B respectively.

Conclusion: In our study, we tried to evaluate the effects of LNG-IUS and dienogest on patients with symptomatic adenomyosis. We found that LNG-IUS is a useful tool for HMB and dysmenorrhea in women of all ages. In our study the LNG-IUD is proved to be an effective approach compared to dienogest to treat adenomyosis. LNG-IUS is a promising and effective option for the management of adenomyosis. Its use effectively reduced the severity of symptoms, uterine volume and endometrial thickness, and improved laboratory outcomes.

Keywords: adenomyosis, dysmenorrhoea, LNG-IUS, dienogest.

Author α: A Department of Medical College Hospital, Bangladesh.
e-mail: drjesminebanu@gmail.com

I. Introduction

Adenomyosis is a common, estrogen-dependent, a benign gynaecological disease characterized by endometrial glands and stroma invading, implanting, and proliferating within the myometrium to form diffuse or localized lesions. [1] Adenomyosis is common in women of childbearing age. The signs and symptoms include dysmenorrhea, menorrhagia, abnormal uterine bleeding, enlarged uterus, dyspareunia, and infertility, which can seriously affect the patient's quality of life. [2] About two-thirds of women who are diagnosed with adenomyosis are symptomatic and the most common symptoms include menorrhagia and dysmenorrhea. [3] The average age of presentation is usually above 40 years, although it can be seen in young women as well. [4] The prevalence of adenomyosis varies widely from 5% to 70%, depending on the method used for diagnosis and the rate of diagnosis during hysterectomy is approximately 20–30%. [5] Adenomyosisis often associated with hormone-dependent lesions such as endometriosis, uterine fibroids andendometrial hyperplasia/ polyps. Despite the prevalence and the severity of symptoms, the pathogenesis and etiology of adenomyosisis yet not clearly understood. Epidemiological data suggest that a large number of births, spontaneous and induced abortions, and endometrial hyperplasia are associated with increased risks of adenomyosis. Other risk factors associated with adenomyosis include endometriosis, surgical trauma, cesarean section or curettage, and smoking. [4,6] Several evidences show the presence of association between infertility and adenomyosis where probable mechanisms involved including impairment of sperm transport, aberrant uterine contractility, alterations of adhesion molecules, cell proliferation, apoptosis, and free radical metabolism. [7] Adenomyosis is one of the causes of recurrent implantation failure during IVF treatment. [8] Traditionally, hysterectomy has been the only definitive treatment for patients with adenomyosis who do not need to preserve fertility. Other minimally invasive surgery like endometrial resection or ablation can improve the symptoms of menorrhagia but often fails to relieve dysmenorrhea. [7,9] At present, other medical treatments using suppressive hormonal treatment, such as oral contraceptive/low-dose estrogen (OC/LEP), danazol, aromatase inhibitor (AI), gonadotropin-releasing hormone analog (GnRH a) have

been used to control symptoms of adenomyosis among women who are unwilling to undergo hysterectomy or who need to preserve fertility. Medical treatments for adenomyosis always follow the principles of the management of endometriosis, which are usually aimed at reducing the production of endogenous estrogen or inducing endometrial differentiation with progestin. The objectives of medical treatment are the inhibition of ovulation, abolition of menstruation, and achievement of a stable steroid hormone milieu, based on the concept that the responses of the eutopic and ectopic endometrium are substantially similar. Drugs used for medical treatment create a hypo estrogenic (GnRH agonists, AIs), hyperandrogenic (danazol, gestrinone) or hyperprogestogenic (OCs, progestins) environment, with suppression of endometrial cell proliferation. [7,10] The levonorgestrel-releasing intrauterine system (LNG-IUS) has been approved in Europe for contraception since 1990. Because of the suppressive effect of levonorgestrel on the endometrium, LNG-IUS has been proven to be effective for the management of menorrhagia and dysmenorrhea. [11] The levonorgestrel-releasing intrauterine system (LNG-IUS), which releases 20mg of levonorgestrel every 24 hours during a 5-year period, has been proven to be effective for menorrhagia and dysmenorrhea. One systemic review and meta-analysis on effect of LNG-IUS on adenomyosis recommend that LNG-IUS is the preferred option over other hormonal therapies given its direct action on the uterus, low systemic levels of steroid hormone and long-acting user independent administration for women with adenomyosis, having desire for pregnancy or refuse hysterectomy as definitive treatment. [3,12] Potential mechanisms of LNG-IUS action are endometrial decidualization and atrophy, reducing endometrial blood flow and a decrease in the number of estrogen receptors in the endometrial glands and stroma. This may further prevent estrogen stimulation of myometrial adenomyosis causing the lesions to atrophy. The subsequent improvements in uterine smooth muscle contractility and reduced menstrual flow may explain the reduction in uterine volume. [13] Moreover, decreased expression of growth factors and the related receptors has been found in women with heavy bleeding and adenomyosis following LNG-IUS treatment. [14] Another randomized study showed a positive effect of LNG-IUS in around 100 women with adenomyosis suffering from heavy menstrual bleeding. Administration of LNG-IUS could reduce average blood loss by 75% in adenomyosis patient with excessive menstruation. LNG-IUS demonstrates significant and comparable improvements in Hb levels to hysterectomy in treating adenomyosis-associated menorrhagia during the first year. Both treatments improve Health-related quality of life (QOL) but LNG-IUS seems to have superior effects on psychological and social life. [13,15] Dienogest, a novel 19-nortestosterone derivative, is a synthetic oral progestin that is highly selective for progesterone receptors. Several studies reported that dienogest is highly effective in reducing adenomyosis related pain. [16] Dienogest suppresses ovarian function and proves highly effective in the treatment of chronic pelvic pain. [17] Dienogest directly inhibits cellular proliferation and induces apoptosis in human adenomyotic cells. [18] It induces a mild hypoestrogenic and a potent local hypergestagenic environment that causes atrophy of endometriotic lesions without severe hypoestrogenic adverse effects. As there is similarity between endometriosis and adenomyosis in hormonal responses, dienogest is used for therapeutic alternative for symptomatic adenomyosis. [19] Hence, there is a strong need to develop well-tolerated medical treatments that provide effective outcomes for symptomatic adenomyosis. Ota et al. did a controlled clinical trial and showed that DNG and LNG-IUS could provide cost-effective, reversible, long-term treatment for patients with symptomatic adenomyosis, reducing the need for surgical intervention. [20] To choose between arrays of regimes of adenomyosis treatment, the impetus depends on patients' condition, facilities available, economic condition and general acceptability of the treatment regime concerned.

So, in this present study we aimed to evaluate and compare the effects of LNG-IUS and Dienogest among the woman with symptomatic adenomyosis.

II. Objective of the Study

The main objective of the study was to evaluate and compare the effectiveness between LNG-IUS and Dienogest among the woman with symptomatic adenomyosis.

III. Methodology & Materials

This was a randomized control clinical trial and was conducted in the Department of Reproductive Endocrinology and Infertility, Bangabandhu Sheikh Mujib Medical University (BSMMU), Shahbag, Dhaka, Bangladesh during the period from ---------- to ----------.

We included 20 patients with symptomatic adenomyosis diagnosis confirmed by transvaginal ultrasound in this study. All patients were divided by sequentially numbered sealed opaque envelops into two groups- Group A & Group B. Among of 20 patients, 10 were in the group A and 10 patients were in the group B. Group A who received LNG-IUS and group B who received dienogest. Tabdinogest 2mg (Nuvista Pharma Ltd)`was administered at a dose of 2 mg once daily for 3 months continuously starting from days 2–5 of menstruation and Eloira (Pregna International, India), LNG-IUS, was implanted in strict accordance with the operating instructions within 7 days of the start of

menstrual flow. The levonorgestrel-releasing intrauterine system (LNG-IUS) releases levonorgestrel 20mcg/day during a 5-year period.

These were the following criteria to be eligible for the enrollment as our study participants: a) Patients who were aged between 25-45 years old; b) Patients with diagnosed case of symptomatic adenomyosis (menorrhagia and dysmenorrhea); c) Patients with uterine length≤ 12 cm determined by ultrasound; d) Patients who were willing to participate in the study; Anda) Patients with any contraindications with LNG-IUS or dienogest; b) Patients with ovarian endometrioma more than 3-cm in diameter; c) Patients with undiagnosed vaginal bleeding; d) Patients with the presence of uterine fibroids, including submucosal fibroids; e) Patients with any acute illness or pelvic inflammation (e.g., renal or hepatic diseases, ischemic heart disease etc.) were excluded from our study.

Adenomyosis was diagnosed by presence of menorrhagia or dysmenorrhoea and based on patients' symptoms, physical examination & transvaginal ultrasonogram. Volume of uterus was measured by ultrasound and response for pain was measured on a visual analog scale (VAS) of 0-10 scale and volume of bleeding (regular, heavy, spotting) at the beginning of treatment and at interval of 3 months.

a) Uterine volume

The uterine volume was calculated using the formula for an ellipsoid (volume = 0.52 × length× anteroposterior diameter × transverse diameter). [21]

b) Menorrhagia

Menorrhagia is defined as heavy menstrual bleeding (HMB) when menstrual blood loss > 80 mL which interferes with a woman's physical, social, emotional and/or material quality of life. (De Cherney, Nathan, Laufer and Roman, 2019). Heavy menstrual bleeding was assessed by number of pads, passage of clots (size and number) and interference of quality of life.

c) VAS scale

The Visual Analogue Scale (VAS) will consist of a straight line of 10 cm with the endpoints defining extreme limits such as 'no pain at all=0' and 'pain as bad as it could be=10'. The patient was asked to mark her pain level on the line between the two endpoints. The distance (in cm) between 'no pain at all' and the 'mark' then will define the subject's pain. A higher score indicates greater pain intensity. Assessment is clearly highly subjective. The VAS was administered as a paper and pencil measure. In this study population, all patients rated their pain on a visual analog scale (vas, 0-10) before treatment and on next occasion, after 3 months of treatment. 0 – means no pain, 1-3 means mild pain, 4-7 means moderate pain, 8-10 means severe pain.

Statistical Analysis: All data were recorded systematically in preformed data collection form and quantitative data was expressed as mean and standard deviation and qualitative data was expressed as frequency distribution and percentage. Statistical analysis was carried out by using Statistical analysis was done by using SPSS (Statistical Package for Social Science) Version 26 for windows 10. Data was tested using paired t-test and chi-square test. P value <0.05 was considered as statistically significant. Ethical clearance was obtained from Institutional Review Board (IRB) of BSMMU to undertake the current study.

IV. Result

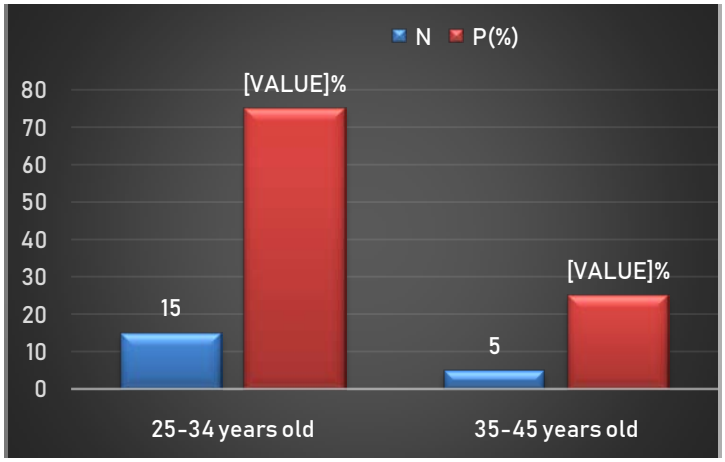


Figure 1: Age distribution among our study people

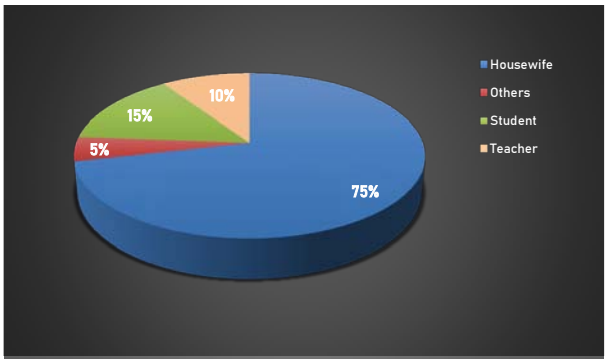


Figure 2: Distribution of our study subjects based on their occupation

Table 1: Baseline demographic characteristics of our study population

Variables	Group A (LNG-IUS)		Group B (Dienogest)		P-value
25-34 years old	5	50%	10	100%	0.01
35-45 years old	5	50%	0	0	
Mean Age (years)	34.80 ± 3.79		28.60 ±3.17		0.09
Educational status					
Illiterate	1	10%	0		0.01
Primary & SSC					
HSC or above	9	90%	10	100%	
BMI(kg/m²)	28.07±2.72		26.06 ± 2.46		0.07
Previous pregnancy	9	90%	5	50%	0.02
Primary subfertility	1	10%	5	50%	0.01
Secondary subfertility	7	70%	3	30%	0.01
Ovarian endometrioma	2	20%	3	30%	0.01

Table 2: Distribution of our study people based on dysmenorrhea & pattern of menstruation

Variables	At Baseline		At 3rd month		*P-value*
	Group A (LNG-IUS)	*Group B (Dienogest)*	*Group A (LNG-IUS)*	*Group B (Dienogest)*	
Dysmenorrhea	10(100%)	10(100%)	8(80%)	9(90%)	0.001
Pattern of menstruation					
Spotting	0	0	0	2(20%)	0.002
Amenorrhea	0	0	2(20%)	2(20%)	0.001
Heavy	8(80%)	8(80%)	0	3(30%)	0.012
Regular	2(20%)	2(20%)	8(80%)	3(30%)	0.080

Table 3: Clinical & Laboratory variables among our study people

Variables	*Group A (LNG-IUS)*	*Group B (Dienogest)*	*P-value*
VAS			
At Baseline	9.10±0.84	8.75 ±1.14	0.000
At 3rd month	1.10 ±1.10	4.30± 2.41	0.012
Hemoglobin level (gm/dl)			
At Baseline	10.87 ±1.42	10.82± 0.64	0.000
At 3rd month	11.57 ±1.33	11.09± 0.53	0.000
Uterine volume (cm^3)			
At Baseline	268.08 ± 118.28	202.32 ±117.76	0.000
At 3rd month	210.10 ±105.49	202.77 ± 118.33	0.000

In this study figure 1 showed the age distribution among our study people. Majority of our patients (75%) were aged between 25 to 34 years old and 25 % were aged between 35 to 45 years old. Here figure 2 showed the distribution of our study subjects based on their occupation. We found that majority of our patients were housewife (75%), 15% were students, 10 % were teachers & 5 % were from other occupation. In table 1 we showed the baseline demographic characteristics of our study population. We found the Mean ± SD of age was 34.80 ± 3.79 & 28.60 ± 3.17 among group A & B respectively. We found the mean of BMI was 28.07± 2.72 & 26.06 ± 2.46 respectively in group A & B. Previous pregnancy was found in 9(90%) & 5(50%) patients among group A & B respectively. We found primary subfertility in 1(10%) & 5(50%) cases of group A & B respectively. Secondary subfertility was found in 7(70%) patients in group A & 3(30%) patients in group B. We found ovarian endometrioma in 2(20%) & 3(30%) patients among group A & B respectively. In table 2 we showed the distribution of our study people based on dysmenorrhea & pattern of menstruation. Before treatment we found dysmenorrhea in 10(100%) patients among both groups. After 3 months interval we found dysmenorrhea 8(80%) & 9(90%) patients in group A & B respectively. Before treatment regular menstruation was found 20% in both groups; heavy menstruation was found 80% & 80% in group A & B respectively. At 3rd month spotting was found 20% in group B; amenorrhea was found 20% in both groups; heavy menstruation was found 30% in group B; regular menstruation was found 80% & 30% in group A & B respectively. Table 3 showed the clinical &laboratory variables among our study people. Before treatment the mean of VAS was 9.10±0.84 & 8.75 ±1.14 in group A & B respectively. At 3rd month the mean of VAS was 1.10 ±1.10 & 4.30± 2.41 among group A & B and we found that pain was significantly lower among group A. Before treatment the mean of hemoglobin level was 10.87 ±1.42 & 10.82±0.64 n group A & B respectively. At 3rd month the mean of hemoglobin level was 11.57 ±1.33 & 11.09± 0.53 among group A & B and we found that hemoglobin level significantly increased among group A compared to group B. Before treatment the mean of uterine volume was 268.08 ± 118.28 & 202.32 ±117.76 in group A & B respectively. At 3rd month we found the mean of uterine volume was 210.10 ±105.49 & 202.77 ± 118.33 among group A & B and we found that uterine volume was significantly decreased among group A compared to group B patients.

V. Discussion

In this study we found the majority of our patients (75%) were aged between 25 to 34 years old and 25 % were aged between 35 to 45 years old. [Figure 1] In our study we found majority of our patients were housewife (75%), 15% were students, 10 % were teachers & 5 % were from other occupation. [Figure 2] We found the Mean ± SD of age was 34.80 ± 3.79 & 28.60 ± 3.17 among group A & B respectively. We found the mean of BMI was 28.07± 2.72 & 26.06 ± 2.46 respectively I group A & B. Previous pregnancy was found in 9(90%) & 5(50%) patients among group A & B respectively. We found primary subfertility in 1(10%) & 5(50%) cases of group A & B respectively. Secondary subfertility was found in 7 patients in group A &3 patients in group B. We found ovarian endometrioma in 2 & 3 patients among group A & B respectively. [Table 1] Before treatment we found dysmenorrhea in 10(100%) patients among both groups. After 3 months interval we found dysmenorrhea 8(80%) & 9(90%) patients in group A & B respectively. Before treatment regular menstruation was found 20% in both groups; heavy menstruation was found 80% & 80% in group A & B respectively. At 3rd month spotting was found 20% in group B; amenorrhea was found 20% in both groups; heavy menstruation was found 30% in group B; regular menstruation was found 80% & 30% in group A & B respectively. [Table 2] A study done by (Fedele et al.) inserted the device in 25 women with recurrent adenomyosis-related menorrhagia. Of the 23 women who completed 12 months of treatment, 2 had become amenorrheic, 3 were oligomenorrheic, 2 reported spotting, and 16 had regular periods. The authors

speculated that the IUS produced decidualization and, subsequently, marked hypotrophy of the eutopic endometrium.[2] Another study (Barrington and Bowen-Simpkins) inserted the LNG-IUS in 50 women awaiting surgery and evaluated menstrual loss using a pictorial chart, a full blood count, and the measurement of ferritin. [22] By nine months post-insertion, bleeding was reduced to acceptable levels in 41 cases, with 4 subjects developing amenorrhea. These results were subsequently confirmed in larger cohorts. [9,23]

Before treatment the mean of VAS was 9.10±0.84 & 8.75 ±1.14 in group A & B respectively. At 3rd month the mean of VAS was 1.10 ±1.10 & 4.30± 2.41 among group A & B and we found that pain was significantly lower among group A. Before treatment the mean of hemoglobin level was 10.87 ±1.42 & 10.82±0.64 n group A & B respectively. At 3rd month the mean of hemoglobin level was 11.57 ±1.33 & 11.09± 0.53 among group A & B and we found that hemoglobin level significantly increased among group A compared to group B. Before treatment the mean of uterine volume was 268.08 ± 118.28 & 202.32 ±117.76 in group A & B respectively. At 3rd month the mean of uterine volume was 210.10 ±105.49 & 202.77 ± 118.33 among group A & B and we found that uterine volume was significantly decreased among group A compared to group B patients. [Table 3] A study done by (Yang et al.) showed that dienogest was more effective at relieving pain than LNG-IUS. After 3 months of treatment with dienogest, the patients' VAS score decreased from (8.76 ± 0.97) to (5.39 ± 1.07), and pain control was more stable with extended duration of treatment. Dienogest also produced better control of dyspareunia and pelvic pain, symptoms that were poorly controlled by LNG-IUS, with a significant reduction in scores from (5.24 ± 0.86) to (1.37 ± 0.66) following 12 months of treatment.[24] These results are not consistent with our findings. (Yang et al.) also added that LNG-IUS was effective in reducing uterine volume in patients with adenomyosis, while dienogest demonstrated a modest effect in reducing uterine volume. [24] This finding is consistent with the findings of our study. Another randomized double-blind multicenter controlled study done by (Osuga et al.) found that 130 patients with symptomatic adenomyosis who adhered to 2 mg/d dienogest for 52 weeks had a significant decrease in pain level scores and a decrease in the frequency of analgesic use. The pain scores decreased to (3.4 ± 1.8) at 24 weeks, and (3.8 ± 1.5) at 52 weeks, compared to baseline, indicating a more significant relief of dysmenorrhea in patients with symptomatic adenomyosis with long-term use of dienogest. [17] Clear advantages exist in treatment with the LNG-IUS in adolescents with HMB, dysmenorrhea, and pelvic pain/endometriosis, and, indeed, good results have been reported in young women with AUB, dysmenorrhea, and pelvic pain related to endometriosis, which is similar to our findings. [25]

VI. Limitations of the Study

Our study was a single centre study. We studied the effects of LNG-IUS & Dienogest on a few variables within a short study period. There are more variables of adenomyosis to be evaluated to know the effectiveness between LNG-IUS & Dienogest. After evaluating once those patients we could only follow-up them for 3 months and have not known other possible interference that may happen in the long term with these patients.

VII. Conclusion and Recommendations

In our study, we tried to evaluate the effects of LNG-IUS and dienogest on patients with symptomatic adenomyosis. We found that LNG-IUS is a useful tool for HMB and dysmenorrheain women of all ages. In our study the LNG-IUD is proved to be an effective approach compared to dienogest to treat adenomyosis. LNG-IUS is a promising and effective option for the management of adenomyosis. Its use effectively reduced the severity of symptoms, uterine volume and improved laboratory outcomes.

So further study with a retrospective and longitudinal study design including larger sample size needs to be done to increase the evidence-based knowledge about the effectiveness of these drugs which will help the clinicians to find an effective and safer medical treatment of adenomyosis.

References Références Referencias

1. Chen, S., Wang, J., Sun, W., Zhu, L., He, J. and Zhang, X., 2020. Efficacy of the levonorgestrel-releasing intrauterine device is associated with different subtypes of adenomyosis: a retrospective study. Annals of Translational Medicine, 8(21).
2. Fedele, L., Bianchi, S., Raffaelli, R., Portuese, A. and Dorta, M., 1997. Treatment of adenomyosis-associated menorrhagia with a levonorgestrel-releasing intrauterine device. Fertility and sterility, 68(3), pp.426-429.
3. Song, S.Y., Lee, S.Y., Kim, H.Y., Park, D.B., Lee, K.H., Lee, S., Yang, J.B. and Yoo, H.J., 2020. Long-term efficacy and feasibility of levonorgestrel-releasing intrauterine device use in patients with adenomyosis. Medicine, 99(22), p.e20421.
4. Rapkin AJ, Nathan L. Pelvic pain and dysmenorrhea.2012
5. Cunningham, R.K., Horrow, M.M., Smith, R.J. and Springer, J., 2018. Adenomyosis: a sonographic diagnosis. Radiographics, 38(5), pp.1576-1589.
6. Vercellini, P., Viganò, P., Somigliana, E. and Fedele, L., 2014. Endometriosis: pathogenesis and

treatment. Nature Reviews Endocrinology, 10(5), pp.261-275.
7. Li, J.J., Chung, J.P., Wang, S., Li, T.C. and Duan, H., 2018. The investigation and management of adenomyosis in women who wish to improve or preserve fertility. Bio Med research international, 2018.
8. Tremellen, K. and Russell, P., 2011. Adenomyosis is a potential cause of recurrent implantation failure during IVF treatment. Australian and New Zealand Journal of Obstetrics and Gynaec
9. Peng, F.S., Wu, M.Y., Yang, J.H., Chen, S.U., Ho, H.N. and Yang, Y.S., 2010. Insertion of the Mirena intrauterine system for treatment of adenomyosis-associated menorrhagia: a novel method. Taiwanese journal of obstetrics and gynecology, 49(2), pp.160-164.
10. Tsui, K.H., Lee, W.L., Chen, C.Y., Sheu, B.C., Yen, M.S., Chang, T.C. and Wang, P.H., 2014. Medical treatment for adenomyosis and/or adenomyoma. Taiwanese Journal of Obstetrics and Gynecology, 53(4), pp.459-465.
11. Irvine, G.A., Campbell-Brown, M.B., Lumsden, M.A., Heikkilä, A., Walker, J.J. and Cameron, I.T., 1998. Randomized comparative trial of the intrauterine system and norethisteronelevonorgestrel for treatment of idiopathic menorrhagia. BJOG: An International Journal of Obstetrics & Gynecology, 105(6), pp.592-598.
12. Abbas, A.M., Samy, A., Atwa, K., Ghoneim, H.M., Lotfy, M., Saber Mohammed, H., Abdellah, A.M., El Bahie, A.M., Aboelroose, A.A., El Gedawy, A.M. and Mostafa, M., 2020. The role of levonorgestrel intra-uterine system in the management of adenomyosis: A systematic review and meta-analysis of prospective studies. Actaobstetricia et gynecologica Scandinavica, 99(5), pp.571-581.
13. Zhang, P., Song, K., Li, L., Yukuwa, K. and Kong, B., 2013. Efficacy of combined levonorgestrel-releasing intrauterine system with gonadotropin-releasing hormone analog for the treatment of adenomyosis. Medical Principles and Practice, 22(5), pp.480-483.
14. Choi, Y.S., Cho, S., Lim, K.J., Jeon, Y.E., Yang, H.I., Lee, K.E., Heena, K., Seo, S.K., Kim, H.Y. and Lee, B.S., 2010. Effects of LNG-IUS on nerve growth factor and its receptors expression in patients with adenomyosis. Growth Factors, 28(6), pp.452-460.
15. Ozdegirmenci, O., Kayikcioglu, F., Akgul, M.A., Kaplan, M., Karcaaltincaba, M., Haberal, A. and Akyol, M., 2011. Comparison of levonorgestrel intrauterine system versus hysterectomy on efficacy and quality of life in patients with adenomyosis. Fertility and sterility, 95(2), pp.497-502.
16. Neriishi, K., Hirata, T., Fukuda, S., Izumi, G., Nakazawa, A., Yamamoto, N., Harada, M., Hirota, Y., Koga, K., Wada-Hiraike, O. and Fujii, T., 2018. Long-term dienogest administration in patients with symptomatic adenomyosis. Journal of Obstetrics and Gynaecology Research, 44(8), pp.1439-1444.
17. Osuga, Y., Fujimoto-Okabe, H. and Hagino, A., 2017. Evaluation of the efficacy and safety of dienogest in the treatment of painful symptoms in patients with adenomyosis: a randomized, double-blind, multicenter, placebo-controlled study. Fertility and sterility, 108(4), pp.673-678.
18. Yamanaka, A., Kimura, F., Kishi, Y., Takahashi, K., Suginami, H., Shimizu, Y. and Murakami, T., 2014. Progesterone and synthetic progestin, dienogest, induce apoptosis of human primary cultures of adenomyotic stromal cells. European Journal of Obstetrics & Gynecology and Reproductive Biology, 179, pp.170-174.
19. Schindler, A.E., 2011. Dienogest in long-term treatment of endometriosis. International journal of women's health, 3, p.175.
20. Ota, I., Taniguchi, F., Ota, Y., Nagata, H., Wada, I., Nakaso, T., Ikebuchi, A., Sato, E., Azuma, Y. and Harada, T., 2021. A controlled clinical trial comparing potent progestins, LNG-IUS and dienogest, for the treatment of women with adenomyosis. Reproductive Medicine and Biology, 20(4), pp.427-434.
21. Park, D.S., Kim, M.L., Song, T., Yun, B.S., Kim, M.K., Jun, H.S. and Seong, S.J., 2015. Clinical experiences of the levonorgestrel-releasing intrauterine system in patients with large symptomatic adenomyosis. Taiwanese Journal of Obstetrics and Gynecology, 54(4), pp.412-415.
22. Brosens, I.A. Endometriosis—A disease because it is characterized by bleeding. Am. J. Obstet. Gynecol. 1997, 176, 263–267.
23. Barrington, J.W.; Bowen-Simpkins, P. The levonorgestrel intrauterine system in the management of menorrhagia. BJOG Int. J. Obstet. Gynaecol. 1997, 104, 614–616.
24. Yang S, Liu Y, Wen J, Sun Y, Ren F. Clinical Efficacy of Dienogest versus Levonorgestrel-Releasing Intrauterine System for Adenomyosis. Evid Based Complement Alternat Med. 2022 Jul 15; 2022: 1995472.
25. Bayer, L.L.; Hillard, P.J.A. Use of Levonorgestrel Intrauterine System for Medical Indications in Adolescents. J. Adolesc. Health.2013, 52, S54–S58.

Global Journals Guidelines Handbook 2023

www.GlobalJournals.org

Memberships

Fellows/Associates of Medical Research Council

FMRC/AMRC Memberships

Introduction

FMRC/AMRC is the most prestigious membership of Global Journals accredited by Open Association of Research Society, U.S.A (OARS). The credentials of Fellow and Associate designations signify that the researcher has gained the knowledge of the fundamental and high-level concepts, and is a subject matter expert, proficient in an expertise course covering the professional code of conduct, and follows recognized standards of practice. The credentials are designated only to the researchers, scientists, and professionals that have been selected by a rigorous process by our Editorial Board and Management Board.

Associates of FMRC/AMRC are scientists and researchers from around the world are working on projects/researches that have huge potentials. Members support Global Journals' mission to advance technology for humanity and the profession.

FMRC

Fellow of Medical Research Council

FELLOW OF MEDICAL RESEARCH COUNCIL is the most prestigious membership of Global Journals. It is an award and membership granted to individuals that the Open Association of Research Society judges to have made a 'substantial contribution to the improvement of computer science, technology, and electronics engineering.

The primary objective is to recognize the leaders in research and scientific fields of the current era with a global perspective and to create a channel between them and other researchers for better exposure and knowledge sharing. Members are most eminent scientists, engineers, and technologists from all across the world. Fellows are elected for life through a peer review process on the basis of excellence in the respective domain. There is no limit on the number of new nominations made in any year. Each year, the Open Association of Research Society elect up to 12 new Fellow Members.

To the institution

Get letter of appreciation

Global Journals sends a letter of appreciation of author to the Dean or CEO of the University or Company of which author is a part, signed by editor in chief or chief author.

Exclusive Network

Get access to a closed network

A FMRC member gets access to a closed network of Tier 1 researchers and scientists with direct communication channel through our website. Fellows can reach out to other members or researchers directly. They should also be open to reaching out by other.

Career | Credibility | Exclusive | Reputation

Certificate

Certificate, LoR and Laser-Momento

Fellows receive a printed copy of a certificate signed by our Chief Author that may be used for academic purposes and a personal recommendation letter to the dean of member's university.

Career | Credibility | Exclusive | Reputation

Designation

Get honored title of membership

Fellows can use the honored title of membership. The “FMRC” is an honored title which is accorded to a person’s name viz. Dr. John E. Hall, Ph.D., FMRC or William Walldroff, M.S., FMRC.

Career | Credibility | Exclusive | Reputation

Recognition on the Platform

Better visibility and citation

All the Fellow members of FMRC get a badge of "Leading Member of Global Journals" on the Research Community that distinguishes them from others. Additionally, the profile is also partially maintained by our team for better visibility and citation. All fellows get a dedicated page on the website with their biography.

Career | Credibility | Reputation

Future Work

Get discounts on the future publications

Fellows receive discounts on the future publications with Global Journals up to 60%. Through our recommendation programs, members also receive discounts on publications made with OARS affiliated organizations.

Career | Financial

GJ Internal Account

Unlimited forward of Emails

Fellows get secure and fast GJ work emails with unlimited storage of emails that they may use them as their primary email. For example,
john [AT] globaljournals [DOT] org.

Career | Credibility | Reputation

Premium Tools

Access to all the premium tools

To take future researches to the zenith, fellows receive access to all the premium tools that Global Journals have to offer along with the partnership with some of the best marketing leading tools out there.

Financial

Conferences & Events

Organize seminar/conference

Fellows are authorized to organize symposium/seminar/conference on behalf of Global Journal Incorporation (USA). They can also participate in the same organized by another institution as representative of Global Journal. In both the cases, it is mandatory for him to discuss with us and obtain our consent. Additionally, they get free research conferences (and others) alerts.

Career | Credibility | Financial

Early Invitations

Early invitations to all the symposiums, seminars, conferences

All fellows receive the early invitations to all the symposiums, seminars, conferences and webinars hosted by Global Journals in their subject.

Exclusive

Publishing Articles & Books

Earn 60% of sales proceeds

Fellows can publish articles (limited) without any fees. Also, they can earn up to 70% of sales proceeds from the sale of reference/review books/literature/publishing of research paper. The FMRC member can decide its price and we can help in making the right decision.

Exclusive | Financial

Reviewers

Get a remuneration of 15% of author fees

Fellow members are eligible to join as a paid peer reviewer at Global Journals Incorporation (USA) and can get a remuneration of 15% of author fees, taken from the author of a respective paper.

Financial

Access to Editorial Board

Become a member of the Editorial Board

Fellows and Associates may join as a member of the Editorial Board of Global Journals Incorporation (USA) after successful completion of three years as Fellow and as Peer Reviewer.

Career | Credibility | Exclusive | Reputation

And Much More

Get access to scientific museums and observatories across the globe

All members get access to 5 selected scientific museums and observatories across the globe. All researches published with Global Journals will be kept under deep archival facilities across regions for future protections and disaster recovery. They get 10 GB free secure cloud access for storing research files.

ASSOCIATE OF MEDICAL RESEARCH COUNCIL

ASSOCIATE OF MEDICAL RESEARCH COUNCIL is the membership of Global Journals awarded to individuals that the Open Association of Research Society judges to have made a 'substantial contribution to the improvement of computer science, technology, and electronics engineering.

The primary objective is to recognize the leaders in research and scientific fields of the current era with a global perspective and to create a channel between them and other researchers for better exposure and knowledge sharing. Members are most eminent scientists, engineers, and technologists from all across the world. Associate membership can later be promoted to Fellow Membership. Associates are elected for life through a peer review process on the basis of excellence in the respective domain. There is no limit on the number of new nominations made in any year. Each year, the Open Association of Research Society elect up to 12 new Associate Members.

To the institution

Get letter of appreciation

Global Journals sends a letter of appreciation of author to the Dean or CEO of the University or Company of which author is a part, signed by editor in chief or chief author.

Exclusive Network

Get access to a closed network

A AMRC member gets access to a closed network of Tier 2 researchers and scientists with direct communication channel through our website. Associates can reach out to other members or researchers directly. They should also be open to reaching out by other.

Career | Credibility | Exclusive | Reputation

Certificate

Certificate, LoR and Laser-Momento

Associates receive a printed copy of a certificate signed by our Chief Author that may be used for academic purposes and a personal recommendation letter to the dean of member's university.

Career | Credibility | Exclusive | Reputation

Designation

Get honored title of membership

Associates can use the honored title of membership. The “AMRC” is an honored title which is accorded to a person’s name viz. Dr. John E. Hall, Ph.D., AMRC or William Walldroff, M.S., AMRC.

Career | Credibility | Exclusive | Reputation

Recognition on the Platform

Better visibility and citation

All the Associate members of AMRC get a badge of "Leading Member of Global Journals" on the Research Community that distinguishes them from others. Additionally, the profile is also partially maintained by our team for better visibility and citation.

Career | Credibility | Reputation

Future Work

Get discounts on the future publications

Associates receive discounts on future publications with Global Journals up to 30%. Through our recommendation programs, members also receive discounts on publications made with OARS affiliated organizations.

Career | Financial

GJ Account

Unlimited forward of Emails

Associates get secure and fast GJ work emails with 5GB forward of emails that they may use them as their primary email. For example,
john [AT] globaljournals [DOT] org.

Career | Credibility | Reputation

Premium Tools

Access to all the premium tools

To take future researches to the zenith, fellows receive access to almost all the premium tools that Global Journals have to offer along with the partnership with some of the best marketing leading tools out there.

Financial

Conferences & Events

Organize seminar/conference

Associates are authorized to organize symposium/seminar/conference on behalf of Global Journal Incorporation (USA). They can also participate in the same organized by another institution as representative of Global Journal. In both the cases, it is mandatory for him to discuss with us and obtain our consent. Additionally, they get free research conferences (and others) alerts.

Career | Credibility | Financial

Early Invitations

Early invitations to all the symposiums, seminars, conferences

All associates receive the early invitations to all the symposiums, seminars, conferences and webinars hosted by Global Journals in their subject.

Exclusive

Publishing Articles & Books

Earn 60% of sales proceeds

Associates can publish articles (limited) without any fees. Also, they can earn up to 30-40% of sales proceeds from the sale of reference/review books/literature/publishing of research paper

Exclusive | Financial

Reviewers

Get a remuneration of 15% of author fees

Associate members are eligible to join as a paid peer reviewer at Global Journals Incorporation (USA) and can get a remuneration of 15% of author fees, taken from the author of a respective paper.

Financial

And Much More

Get access to scientific museums and observatories across the globe

All members get access to 2 selected scientific museums and observatories across the globe. All researches published with Global Journals will be kept under deep archival facilities across regions for future protections and disaster recovery. They get 5 GB free secure cloud access for storing research files.

Associate	Fellow	Research Group	Basic
$4800 **lifetime designation**	$6800 **lifetime designation**	$12500.00 **organizational**	APC **per article**
Certificate, LoR and Momento **2** discounted publishing/year **Gradation** of Research **10** research contacts/day **1 GB** Cloud Storage **GJ** Community Access	**Certificate,** LoR and Momento **Unlimited** discounted publishing/year **Gradation** of Research **Unlimited** research contacts/day **5 GB** Cloud Storage **Online Presense** Assistance **GJ** Community Access	**Certificates,** LoRs and Momentos **Unlimited** free publishing/year **Gradation** of Research **Unlimited** research contacts/day **Unlimited** Cloud Storage **Online Presense** Assistance **GJ** Community Access	**GJ** Community Access

Preferred Author Guidelines

We accept the manuscript submissions in any standard (generic) format.

We typeset manuscripts using advanced typesetting tools like Adobe In Design, CorelDraw, TeXnicCenter, and TeXStudio. We usually recommend authors submit their research using any standard format they are comfortable with, and let Global Journals do the rest.

Alternatively, you can download our basic template from https://globaljournals.org/Template

Authors should submit their complete paper/article, including text illustrations, graphics, conclusions, artwork, and tables. Authors who are not able to submit manuscript using the form above can email the manuscript department at submit@globaljournals.org or get in touch with chiefeditor@globaljournals.org if they wish to send the abstract before submission.

Before and during Submission

Authors must ensure the information provided during the submission of a paper is authentic. Please go through the following checklist before submitting:

1. Authors must go through the complete author guideline and understand and *agree to Global Journals' ethics and code of conduct,* along with author responsibilities.
2. Authors must accept the privacy policy, terms, and conditions of Global Journals.
3. Ensure corresponding author's email address and postal address are accurate and reachable.
4. Manuscript to be submitted must include keywords, an abstract, a paper title, co-author(s') names and details (email address, name, phone number, and institution), figures and illustrations in vector format including appropriate captions, tables, including titles and footnotes, a conclusion, results, acknowledgments and references.
5. Authors should submit paper in a ZIP archive if any supplementary files are required along with the paper.
6. Proper permissions must be acquired for the use of any copyrighted material.
7. Manuscript submitted *must not have been submitted or published elsewhere* and all authors must be aware of the submission.

Declaration of Conflicts of Interest

It is required for authors to declare all financial, institutional, and personal relationships with other individuals and organizations that could influence (bias) their research.

Policy on Plagiarism

Plagiarism is not acceptable in Global Journals submissions at all.

Plagiarized content will not be considered for publication. We reserve the right to inform authors' institutions about plagiarism detected either before or after publication. If plagiarism is identified, we will follow COPE guidelines:

Authors are solely responsible for all the plagiarism that is found. The author must not fabricate, falsify or plagiarize existing research data. The following, if copied, will be considered plagiarism:

- Words (language)
- Ideas
- Findings
- Writings
- Diagrams
- Graphs
- Illustrations
- Lectures

- Printed material
- Graphic representations
- Computer programs
- Electronic material
- Any other original work

Authorship Policies

Global Journals follows the definition of authorship set up by the Open Association of Research Society, USA. According to its guidelines, authorship criteria must be based on:

1. Substantial contributions to the conception and acquisition of data, analysis, and interpretation of findings.
2. Drafting the paper and revising it critically regarding important academic content.
3. Final approval of the version of the paper to be published.

Changes in Authorship

The corresponding author should mention the name and complete details of all co-authors during submission and in manuscript. We support addition, rearrangement, manipulation, and deletions in authors list till the early view publication of the journal. We expect that corresponding author will notify all co-authors of submission. We follow COPE guidelines for changes in authorship.

Copyright

During submission of the manuscript, the author is confirming an exclusive license agreement with Global Journals which gives Global Journals the authority to reproduce, reuse, and republish authors' research. We also believe in flexible copyright terms where copyright may remain with authors/employers/institutions as well. Contact your editor after acceptance to choose your copyright policy. You may follow this form for copyright transfers.

Appealing Decisions

Unless specified in the notification, the Editorial Board's decision on publication of the paper is final and cannot be appealed before making the major change in the manuscript.

Acknowledgments

Contributors to the research other than authors credited should be mentioned in Acknowledgments. The source of funding for the research can be included. Suppliers of resources may be mentioned along with their addresses.

Declaration of funding sources

Global Journals is in partnership with various universities, laboratories, and other institutions worldwide in the research domain. Authors are requested to disclose their source of funding during every stage of their research, such as making analysis, performing laboratory operations, computing data, and using institutional resources, from writing an article to its submission. This will also help authors to get reimbursements by requesting an open access publication letter from Global Journals and submitting to the respective funding source.

Preparing your Manuscript

Authors can submit papers and articles in an acceptable file format: MS Word (doc, docx), LaTeX (.tex, .zip or .rar including all of your files), Adobe PDF (.pdf), rich text format (.rtf), simple text document (.txt), Open Document Text (.odt), and Apple Pages (.pages). Our professional layout editors will format the entire paper according to our official guidelines. This is one of the highlights of publishing with Global Journals—authors should not be concerned about the formatting of their paper. Global Journals accepts articles and manuscripts in every major language, be it Spanish, Chinese, Japanese, Portuguese, Russian, French, German, Dutch, Italian, Greek, or any other national language, but the title, subtitle, and abstract should be in English. This will facilitate indexing and the pre-peer review process.

The following is the official style and template developed for publication of a research paper. Authors are not required to follow this style during the submission of the paper. It is just for reference purposes.

Manuscript Style Instruction (Optional)

- Microsoft Word Document Setting Instructions.
- Font type of all text should be Swis721 Lt BT.
- Page size: 8.27" x 11'", left margin: 0.65, right margin: 0.65, bottom margin: 0.75.
- Paper title should be in one column of font size 24.
- Author name in font size of 11 in one column.
- Abstract: font size 9 with the word "Abstract" in bold italics.
- Main text: font size 10 with two justified columns.
- Two columns with equal column width of 3.38 and spacing of 0.2.
- First character must be three lines drop-capped.
- The paragraph before spacing of 1 pt and after of 0 pt.
- Line spacing of 1 pt.
- Large images must be in one column.
- The names of first main headings (Heading 1) must be in Roman font, capital letters, and font size of 10.
- The names of second main headings (Heading 2) must not include numbers and must be in italics with a font size of 10.

Structure and Format of Manuscript

The recommended size of an original research paper is under 15,000 words and review papers under 7,000 words. Research articles should be less than 10,000 words. Research papers are usually longer than review papers. Review papers are reports of significant research (typically less than 7,000 words, including tables, figures, and references)

A research paper must include:

a) A title which should be relevant to the theme of the paper.
b) A summary, known as an abstract (less than 150 words), containing the major results and conclusions.
c) Up to 10 keywords that precisely identify the paper's subject, purpose, and focus.
d) An introduction, giving fundamental background objectives.
e) Resources and techniques with sufficient complete experimental details (wherever possible by reference) to permit repetition, sources of information must be given, and numerical methods must be specified by reference.
f) Results which should be presented concisely by well-designed tables and figures.
g) Suitable statistical data should also be given.
h) All data must have been gathered with attention to numerical detail in the planning stage.

Design has been recognized to be essential to experiments for a considerable time, and the editor has decided that any paper that appears not to have adequate numerical treatments of the data will be returned unrefereed.

i) Discussion should cover implications and consequences and not just recapitulate the results; conclusions should also be summarized.
j) There should be brief acknowledgments.
k) There ought to be references in the conventional format. Global Journals recommends APA format.

Authors should carefully consider the preparation of papers to ensure that they communicate effectively. Papers are much more likely to be accepted if they are carefully designed and laid out, contain few or no errors, are summarizing, and follow instructions. They will also be published with much fewer delays than those that require much technical and editorial correction.

The Editorial Board reserves the right to make literary corrections and suggestions to improve brevity.

Format Structure

It is necessary that authors take care in submitting a manuscript that is written in simple language and adheres to published guidelines.

All manuscripts submitted to Global Journals should include:

Title

The title page must carry an informative title that reflects the content, a running title (less than 45 characters together with spaces), names of the authors and co-authors, and the place(s) where the work was carried out.

Author details

The full postal address of any related author(s) must be specified.

Abstract

The abstract is the foundation of the research paper. It should be clear and concise and must contain the objective of the paper and inferences drawn. It is advised to not include big mathematical equations or complicated jargon.

Many researchers searching for information online will use search engines such as Google, Yahoo or others. By optimizing your paper for search engines, you will amplify the chance of someone finding it. In turn, this will make it more likely to be viewed and cited in further works. Global Journals has compiled these guidelines to facilitate you to maximize the web-friendliness of the most public part of your paper.

Keywords

A major lynchpin of research work for the writing of research papers is the keyword search, which one will employ to find both library and internet resources. Up to eleven keywords or very brief phrases have to be given to help data retrieval, mining, and indexing.

One must be persistent and creative in using keywords. An effective keyword search requires a strategy: planning of a list of possible keywords and phrases to try.

Choice of the main keywords is the first tool of writing a research paper. Research paper writing is an art. Keyword search should be as strategic as possible.

One should start brainstorming lists of potential keywords before even beginning searching. Think about the most important concepts related to research work. Ask, “What words would a source have to include to be truly valuable in a research paper?” Then consider synonyms for the important words.

It may take the discovery of only one important paper to steer in the right keyword direction because, in most databases, the keywords under which a research paper is abstracted are listed with the paper.

Numerical Methods

Numerical methods used should be transparent and, where appropriate, supported by references.

Abbreviations

Authors must list all the abbreviations used in the paper at the end of the paper or in a separate table before using them.

Formulas and equations

Authors are advised to submit any mathematical equation using either MathJax, KaTeX, or LaTeX, or in a very high-quality image.

Tables, Figures, and Figure Legends

Tables: Tables should be cautiously designed, uncrowned, and include only essential data. Each must have an Arabic number, e.g., Table 4, a self-explanatory caption, and be on a separate sheet. Authors must submit tables in an editable format and not as images. References to these tables (if any) must be mentioned accurately.

Figures

Figures are supposed to be submitted as separate files. Always include a citation in the text for each figure using Arabic numbers, e.g., Fig. 4. Artwork must be submitted online in vector electronic form or by emailing it.

Preparation of Eletronic Figures for Publication

Although low-quality images are sufficient for review purposes, print publication requires high-quality images to prevent the final product being blurred or fuzzy. Submit (possibly by e-mail) EPS (line art) or TIFF (halftone/ photographs) files only. MS PowerPoint and Word Graphics are unsuitable for printed pictures. Avoid using pixel-oriented software. Scans (TIFF only) should have a resolution of at least 350 dpi (halftone) or 700 to 1100 dpi (line drawings). Please give the data for figures in black and white or submit a Color Work Agreement form. EPS files must be saved with fonts embedded (and with a TIFF preview, if possible).

For scanned images, the scanning resolution at final image size ought to be as follows to ensure good reproduction: line art: >650 dpi; halftones (including gel photographs): >350 dpi; figures containing both halftone and line images: >650 dpi.

Color charges: Authors are advised to pay the full cost for the reproduction of their color artwork. Hence, please note that if there is color artwork in your manuscript when it is accepted for publication, we would require you to complete and return a Color Work Agreement form before your paper can be published. Also, you can email your editor to remove the color fee after acceptance of the paper.

Tips for writing a good quality Medical Research Paper

1. Choosing the topic: In most cases, the topic is selected by the interests of the author, but it can also be suggested by the guides. You can have several topics, and then judge which you are most comfortable with. This may be done by asking several questions of yourself, like "Will I be able to carry out a search in this area? Will I find all necessary resources to accomplish the search? Will I be able to find all information in this field area?" If the answer to this type of question is "yes," then you ought to choose that topic. In most cases, you may have to conduct surveys and visit several places. Also, you might have to do a lot of work to find all the rises and falls of the various data on that subject. Sometimes, detailed information plays a vital role, instead of short information. Evaluators are human: The first thing to remember is that evaluators are also human beings. They are not only meant for rejecting a paper. They are here to evaluate your paper. So present your best aspect.

2. Think like evaluators: If you are in confusion or getting demotivated because your paper may not be accepted by the evaluators, then think, and try to evaluate your paper like an evaluator. Try to understand what an evaluator wants in your research paper, and you will automatically have your answer. Make blueprints of paper: The outline is the plan or framework that will help you to arrange your thoughts. It will make your paper logical. But remember that all points of your outline must be related to the topic you have chosen.

3. Ask your guides: If you are having any difficulty with your research, then do not hesitate to share your difficulty with your guide (if you have one). They will surely help you out and resolve your doubts. If you can't clarify what exactly you require for your work, then ask your supervisor to help you with an alternative. He or she might also provide you with a list of essential readings.

4. Use of computer is recommended: As you are doing research in the field of medical research then this point is quite obvious. Use right software: Always use good quality software packages. If you are not capable of judging good software, then you can lose the quality of your paper unknowingly. There are various programs available to help you which you can get through the internet.

5. Use the internet for help: An excellent start for your paper is using Google. It is a wondrous search engine, where you can have your doubts resolved. You may also read some answers for the frequent question of how to write your research paper or find a model research paper. You can download books from the internet. If you have all the required books, place importance on reading, selecting, and analyzing the specified information. Then sketch out your research paper. Use big pictures: You may use encyclopedias like Wikipedia to get pictures with the best resolution. At Global Journals, you should strictly follow here.

6. Bookmarks are useful: When you read any book or magazine, you generally use bookmarks, right? It is a good habit which helps to not lose your continuity. You should always use bookmarks while searching on the internet also, which will make your search easier.

7. Revise what you wrote: When you write anything, always read it, summarize it, and then finalize it.

8. Make every effort: Make every effort to mention what you are going to write in your paper. That means always have a good start. Try to mention everything in the introduction—what is the need for a particular research paper. Polish your work with good writing skills and always give an evaluator what he wants. Make backups: When you are going to do any important thing like making a research paper, you should always have backup copies of it either on your computer or on paper. This protects you from losing any portion of your important data.

9. Produce good diagrams of your own: Always try to include good charts or diagrams in your paper to improve quality. Using several unnecessary diagrams will degrade the quality of your paper by creating a hodgepodge. So always try to include diagrams which were made by you to improve the readability of your paper. Use of direct quotes: When you do research relevant to literature, history, or current affairs, then use of quotes becomes essential, but if the study is relevant to science, use of quotes is not preferable.

10. Use proper verb tense: Use proper verb tenses in your paper. Use past tense to present those events that have happened. Use present tense to indicate events that are going on. Use future tense to indicate events that will happen in the future. Use of wrong tenses will confuse the evaluator. Avoid sentences that are incomplete.

11. Pick a good study spot: Always try to pick a spot for your research which is quiet. Not every spot is good for studying.

12. Know what you know: Always try to know what you know by making objectives, otherwise you will be confused and unable to achieve your target.

13. Use good grammar: Always use good grammar and words that will have a positive impact on the evaluator; use of good vocabulary does not mean using tough words which the evaluator has to find in a dictionary. Do not fragment sentences. Eliminate one-word sentences. Do not ever use a big word when a smaller one would suffice.

Verbs have to be in agreement with their subjects. In a research paper, do not start sentences with conjunctions or finish them with prepositions. When writing formally, it is advisable to never split an infinitive because someone will (wrongly) complain. Avoid clichés like a disease. Always shun irritating alliteration. Use language which is simple and straightforward. Put together a neat summary.

14. Arrangement of information: Each section of the main body should start with an opening sentence, and there should be a changeover at the end of the section. Give only valid and powerful arguments for your topic. You may also maintain your arguments with records.

15. Never start at the last minute: Always allow enough time for research work. Leaving everything to the last minute will degrade your paper and spoil your work.

16. Multitasking in research is not good: Doing several things at the same time is a bad habit in the case of research activity. Research is an area where everything has a particular time slot. Divide your research work into parts, and do a particular part in a particular time slot.

17. Never copy others' work: Never copy others' work and give it your name because if the evaluator has seen it anywhere, you will be in trouble. Take proper rest and food: No matter how many hours you spend on your research activity, if you are not taking care of your health, then all your efforts will have been in vain. For quality research, take proper rest and food.

18. Go to seminars: Attend seminars if the topic is relevant to your research area. Utilize all your resources.

19. Refresh your mind after intervals: Try to give your mind a rest by listening to soft music or sleeping in intervals. This will also improve your memory. Acquire colleagues: Always try to acquire colleagues. No matter how sharp you are, if you acquire colleagues, they can give you ideas which will be helpful to your research.

20. Think technically: Always think technically. If anything happens, search for its reasons, benefits, and demerits. Think and then print: When you go to print your paper, check that tables are not split, headings are not detached from their descriptions, and page sequence is maintained.

21. Adding unnecessary information: Do not add unnecessary information like "I have used MS Excel to draw graphs." Irrelevant and inappropriate material is superfluous. Foreign terminology and phrases are not apropos. One should never take a broad view. Analogy is like feathers on a snake. Use words properly, regardless of how others use them. Remove quotations. Puns are for kids, not grunt readers. Never oversimplify: When adding material to your research paper, never go for oversimplification; this will definitely irritate the evaluator. Be specific. Never use rhythmic redundancies. Contractions shouldn't be used in a research paper. Comparisons are as terrible as clichés. Give up ampersands, abbreviations, and so on. Remove commas that are not necessary. Parenthetical words should be between brackets or commas. Understatement is always the best way to put forward earth-shaking thoughts. Give a detailed literary review.

22. Report concluded results: Use concluded results. From raw data, filter the results, and then conclude your studies based on measurements and observations taken. An appropriate number of decimal places should be used. Parenthetical remarks are prohibited here. Proofread carefully at the final stage. At the end, give an outline to your arguments. Spot perspectives of further study of the subject. Justify your conclusion at the bottom sufficiently, which will probably include examples.

23. Upon conclusion: Once you have concluded your research, the next most important step is to present your findings. Presentation is extremely important as it is the definite medium though which your research is going to be in print for the rest of the crowd. Care should be taken to categorize your thoughts well and present them in a logical and neat manner. A good quality research paper format is essential because it serves to highlight your research paper and bring to light all necessary aspects of your research.

Informal Guidelines of Research Paper Writing

Key points to remember:

- Submit all work in its final form.
- Write your paper in the form which is presented in the guidelines using the template.
- Please note the criteria peer reviewers will use for grading the final paper.

Final points:

One purpose of organizing a research paper is to let people interpret your efforts selectively. The journal requires the following sections, submitted in the order listed, with each section starting on a new page:

The introduction: This will be compiled from reference matter and reflect the design processes or outline of basis that directed you to make a study. As you carry out the process of study, the method and process section will be constructed like that. The results segment will show related statistics in nearly sequential order and direct reviewers to similar intellectual paths throughout the data that you gathered to carry out your study.

The discussion section:

This will provide understanding of the data and projections as to the implications of the results. The use of good quality references throughout the paper will give the effort trustworthiness by representing an alertness to prior workings.

Writing a research paper is not an easy job, no matter how trouble-free the actual research or concept. Practice, excellent preparation, and controlled record-keeping are the only means to make straightforward progression.

General style:

Specific editorial column necessities for compliance of a manuscript will always take over from directions in these general guidelines.

To make a paper clear: Adhere to recommended page limits.

Mistakes to avoid:

- Insertion of a title at the foot of a page with subsequent text on the next page.
- Separating a table, chart, or figure—confine each to a single page.
- Submitting a manuscript with pages out of sequence.
- In every section of your document, use standard writing style, including articles ("a" and "the").
- Keep paying attention to the topic of the paper.
- Use paragraphs to split each significant point (excluding the abstract).
- Align the primary line of each section.
- Present your points in sound order.
- Use present tense to report well-accepted matters.
- Use past tense to describe specific results.
- Do not use familiar wording; don't address the reviewer directly. Don't use slang or superlatives.
- Avoid use of extra pictures—include only those figures essential to presenting results.

Title page:

Choose a revealing title. It should be short and include the name(s) and address(es) of all authors. It should not have acronyms or abbreviations or exceed two printed lines.

Abstract: This summary should be two hundred words or less. It should clearly and briefly explain the key findings reported in the manuscript and must have precise statistics. It should not have acronyms or abbreviations. It should be logical in itself. Do not cite references at this point.

An abstract is a brief, distinct paragraph summary of finished work or work in development. In a minute or less, a reviewer can be taught the foundation behind the study, common approaches to the problem, relevant results, and significant conclusions or new questions.

Write your summary when your paper is completed because how can you write the summary of anything which is not yet written? Wealth of terminology is very essential in abstract. Use comprehensive sentences, and do not sacrifice readability for brevity; you can maintain it succinctly by phrasing sentences so that they provide more than a lone rationale. The author can at this moment go straight to shortening the outcome. Sum up the study with the subsequent elements in any summary. Try to limit the initial two items to no more than one line each.

Reason for writing the article—theory, overall issue, purpose.

- Fundamental goal.
- To-the-point depiction of the research.
- Consequences, including definite statistics—if the consequences are quantitative in nature, account for this; results of any numerical analysis should be reported. Significant conclusions or questions that emerge from the research.

Approach:

- Single section and succinct.
- An outline of the job done is always written in past tense.
- Concentrate on shortening results—limit background information to a verdict or two.
- Exact spelling, clarity of sentences and phrases, and appropriate reporting of quantities (proper units, important statistics) are just as significant in an abstract as they are anywhere else.

Introduction:

The introduction should "introduce" the manuscript. The reviewer should be presented with sufficient background information to be capable of comprehending and calculating the purpose of your study without having to refer to other works. The basis for the study should be offered. Give the most important references, but avoid making a comprehensive appraisal of the topic. Describe the problem visibly. If the problem is not acknowledged in a logical, reasonable way, the reviewer will give no attention to your results. Speak in common terms about techniques used to explain the problem, if needed, but do not present any particulars about the protocols here.

The following approach can create a valuable beginning:

- Explain the value (significance) of the study.
- Defend the model—why did you employ this particular system or method? What is its compensation? Remark upon its appropriateness from an abstract point of view as well as pointing out sensible reasons for using it.
- Present a justification. State your particular theory(-ies) or aim(s), and describe the logic that led you to choose them.
- Briefly explain the study's tentative purpose and how it meets the declared objectives.

Approach:

Use past tense except for when referring to recognized facts. After all, the manuscript will be submitted after the entire job is done. Sort out your thoughts; manufacture one key point for every section. If you make the four points listed above, you will need at least four paragraphs. Present surrounding information only when it is necessary to support a situation. The reviewer does not desire to read everything you know about a topic. Shape the theory specifically—do not take a broad view.

As always, give awareness to spelling, simplicity, and correctness of sentences and phrases.

Procedures (methods and materials):

This part is supposed to be the easiest to carve if you have good skills. A soundly written procedures segment allows a capable scientist to replicate your results. Present precise information about your supplies. The suppliers and clarity of reagents can be helpful bits of information. Present methods in sequential order, but linked methodologies can be grouped as a segment. Be concise when relating the protocols. Attempt to give the least amount of information that would permit another capable scientist to replicate your outcome, but be cautious that vital information is integrated. The use of subheadings is suggested and ought to be synchronized with the results section.

When a technique is used that has been well-described in another section, mention the specific item describing the way, but draw the basic principle while stating the situation. The purpose is to show all particular resources and broad procedures so that another person may use some or all of the methods in one more study or referee the scientific value of your work. It is not to be a step-by-step report of the whole thing you did, nor is a methods section a set of orders.

Materials:

Materials may be reported in part of a section or else they may be recognized along with your measures.

Methods:

- Report the method and not the particulars of each process that engaged the same methodology.
- Describe the method entirely.
- To be succinct, present methods under headings dedicated to specific dealings or groups of measures.
- Simplify—detail how procedures were completed, not how they were performed on a particular day.
- If well-known procedures were used, account for the procedure by name, possibly with a reference, and that's all.

Approach:

It is embarrassing to use vigorous voice when documenting methods without using first person, which would focus the reviewer's interest on the researcher rather than the job. As a result, when writing up the methods, most authors use third person passive voice.

Use standard style in this and every other part of the paper—avoid familiar lists, and use full sentences.

What to keep away from:

- Resources and methods are not a set of information.
- Skip all descriptive information and surroundings—save it for the argument.
- Leave out information that is immaterial to a third party.

Results:

The principle of a results segment is to present and demonstrate your conclusion. Create this part as entirely objective details of the outcome, and save all understanding for the discussion.

The page length of this segment is set by the sum and types of data to be reported. Use statistics and tables, if suitable, to present consequences most efficiently.

You must clearly differentiate material which would usually be incorporated in a study editorial from any unprocessed data or additional appendix matter that would not be available. In fact, such matters should not be submitted at all except if requested by the instructor.

Content:

- Sum up your conclusions in text and demonstrate them, if suitable, with figures and tables.
- In the manuscript, explain each of your consequences, and point the reader to remarks that are most appropriate.
- Present a background, such as by describing the question that was addressed by creation of an exacting study.
- Explain results of control experiments and give remarks that are not accessible in a prescribed figure or table, if appropriate.
- Examine your data, then prepare the analyzed (transformed) data in the form of a figure (graph), table, or manuscript.

What to stay away from:

- Do not discuss or infer your outcome, report surrounding information, or try to explain anything.
- Do not include raw data or intermediate calculations in a research manuscript.
- Do not present similar data more than once.
- A manuscript should complement any figures or tables, not duplicate information.
- Never confuse figures with tables—there is a difference.

Approach:

As always, use past tense when you submit your results, and put the whole thing in a reasonable order.

Put figures and tables, appropriately numbered, in order at the end of the report.

If you desire, you may place your figures and tables properly within the text of your results section.

Figures and tables:

If you put figures and tables at the end of some details, make certain that they are visibly distinguished from any attached appendix materials, such as raw facts. Whatever the position, each table must be titled, numbered one after the other, and include a heading. All figures and tables must be divided from the text.

Discussion:

The discussion is expected to be the trickiest segment to write. A lot of papers submitted to the journal are discarded based on problems with the discussion. There is no rule for how long an argument should be.

Position your understanding of the outcome visibly to lead the reviewer through your conclusions, and then finish the paper with a summing up of the implications of the study. The purpose here is to offer an understanding of your results and support all of your conclusions, using facts from your research and generally accepted information, if suitable. The implication of results should be fully described.

Infer your data in the conversation in suitable depth. This means that when you clarify an observable fact, you must explain mechanisms that may account for the observation. If your results vary from your prospect, make clear why that may have happened. If your results agree, then explain the theory that the proof supported. It is never suitable to just state that the data approved the prospect, and let it drop at that. Make a decision as to whether each premise is supported or discarded or if you cannot make a conclusion with assurance. Do not just dismiss a study or part of a study as "uncertain."

Research papers are not acknowledged if the work is imperfect. Draw what conclusions you can based upon the results that you have, and take care of the study as a finished work.

- You may propose future guidelines, such as how an experiment might be personalized to accomplish a new idea.
- Give details of all of your remarks as much as possible, focusing on mechanisms.
- Make a decision as to whether the tentative design sufficiently addressed the theory and whether or not it was correctly restricted. Try to present substitute explanations if they are sensible alternatives.
- One piece of research will not counter an overall question, so maintain the large picture in mind. Where do you go next? The best studies unlock new avenues of study. What questions remain?
- Recommendations for detailed papers will offer supplementary suggestions.

Approach:

When you refer to information, differentiate data generated by your own studies from other available information. Present work done by specific persons (including you) in past tense.

Describe generally acknowledged facts and main beliefs in present tense.

The Administration Rules

Administration Rules to Be Strictly Followed before Submitting Your Research Paper to Global Journals Inc.

Please read the following rules and regulations carefully before submitting your research paper to Global Journals Inc. to avoid rejection.

Segment draft and final research paper: You have to strictly follow the template of a research paper, failing which your paper may get rejected. You are expected to write each part of the paper wholly on your own. The peer reviewers need to identify your own perspective of the concepts in your own terms. Please do not extract straight from any other source, and do not rephrase someone else's analysis. Do not allow anyone else to proofread your manuscript.

Written material: You may discuss this with your guides and key sources. Do not copy anyone else's paper, even if this is only imitation, otherwise it will be rejected on the grounds of plagiarism, which is illegal. Various methods to avoid plagiarism are strictly applied by us to every paper, and, if found guilty, you may be blacklisted, which could affect your career adversely. To guard yourself and others from possible illegal use, please do not permit anyone to use or even read your paper and file.

Criterion for Grading a Research Paper (Compilation) by Global Journals

Please note that following table is only a Grading of "Paper Compilation" and not on "Performed/Stated Research" whose grading solely depends on Individual Assigned Peer Reviewer and Editorial Board Member. These can be available only on request and after decision of Paper. This report will be the property of Global Journals.

Topics	Grades		
	A-B	**C-D**	**E-F**
Abstract	Clear and concise with appropriate content, Correct format. 200 words or below	Unclear summary and no specific data, Incorrect form Above 200 words	No specific data with ambiguous information Above 250 words
Introduction	Containing all background details with clear goal and appropriate details, flow specification, no grammar and spelling mistake, well organized sentence and paragraph, reference cited	Unclear and confusing data, appropriate format, grammar and spelling errors with unorganized matter	Out of place depth and content, hazy format
Methods and Procedures	Clear and to the point with well arranged paragraph, precision and accuracy of facts and figures, well organized subheads	Difficult to comprehend with embarrassed text, too much explanation but completed	Incorrect and unorganized structure with hazy meaning
Result	Well organized, Clear and specific, Correct units with precision, correct data, well structuring of paragraph, no grammar and spelling mistake	Complete and embarrassed text, difficult to comprehend	Irregular format with wrong facts and figures
Discussion	Well organized, meaningful specification, sound conclusion, logical and concise explanation, highly structured paragraph reference cited	Wordy, unclear conclusion, spurious	Conclusion is not cited, unorganized, difficult to comprehend
References	Complete and correct format, well organized	Beside the point, Incomplete	Wrong format and structuring

INDEX

save our planet

Global Journal of Medical Research

Visit us on the Web at www.GlobalJournals.org | www.MedicalResearchJournal.org
or email us at helpdesk@globaljournals.org

ISSN 9755896