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Discovering Thoughts, Inventing Future

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# Amniotic Fluid Volume Disorders: Causes and Effects

By Sultana MT, Laila A & Nasrin UT

*Abstract-* *Background:* Amniotic fluid is the protective liquid contained by the amniotic sac of a gravid uterus. It is necessary for human fetal growth and development. The amniotic fluid volume (AFV) depends on the gestational age. AFV can be altered in various abnormal situations and may lead to many adverse perinatal outcomes.

*Methods:* A retrospective observational study was done on the admitted patients of Maternal Fetal Medicine Unit, Department of Obs and Gynae, Dhaka Medical College Hospital, Bangladesh, during the year 2020. With due permission from department of obs and Gynae and ethical clearance from appropriate committee, records of admitted patients with abnormal amniotic fluid volume were reviewed and analyzed for evaluation of their underlying etiologies and subsequent outcome of these pregnancies.

*Results:* Among total 656 admitted patients 130 (19.8%) had oligohydramnios and 27 (4.1%) had polyhydramnios. 76.9% of oligohydramnios was due to prelabour rupture of membrane. Other associated conditions of oligohydramnios were hypertensive disorders of pregnancy and growth restricted fetus (11.5%), Diabetic disorders (10.0%), Anomalous fetus (8.5%) and undetermined causes (2.3%). Polyhydramnios was mainly associated with fetal anomaly (59.3%) but a little percentage was associated with gestational diabetes (14.8%), multiple pregnancies (11.1%), chorioangioma (3.7%) and undetermined (11.1%) causes.

*Keywords:* *amniotic fluid, ploy hydramnios, oligohydramnios, perinatal outcome, dhaka medical college hospital.*

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# Amniotic Fluid Volume Disorders: Causes and Effects

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***Discussion:*** From the current study and also other studies showed that some abnormalities of pregnancy are almost always present with amniotic fluid volume disorders and subsequently lead to a considerable number of adverse perinatal outcomes.

***Conclusion:*** It is important to keep an eye on amniotic fluid index for better pregnancy outcome.

*Keywords: amniotic fluid, ployhydramnios, oligohydramnios, perinatal outcome, dhaka medical college hospital.*

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## I. Introduction

Amniotic fluid is a clear, yellow fluid which is found within the first 12 days following conception within the amniotic sac. It surrounds the growing baby in the uterus[1]. It is colorless with slight to moderate turbidity. Amniotic fluid is necessary for human fetal growth and development. The fluid volume cushions the fetus, protecting it from mechanical trauma. Its bacteriostatic properties may helps to maintain a sterile intrauterine environment. The space created by the amniotic fluid allows fetal movement and aids in the normal development of both the lungs and the limbs[2,3].

The rate of amniotic fluid production depends on the gestational age. It produced at a rate of 10 mL/week at first trimester, 50-60 mL/week from 19-25 weeks of gestation, so it increases progressively between 10 to 30 weeks of gestation. It measures about <10 mL at 8 weeks, 50 mL at 12 weeks, 400 mL at 20 weeks, 770 mL at 28 weeks, 1 L at 36-38 weeks. But after 36 weeks, volume decreases at a rate of 60 mL/week at 40 weeks gestation, so it measures 600-800 mL at 40weeks and subsequently 33% decline in volume per week[3].

Ultrasound is a safe method to estimate the AFV. A number of techniques to measure AFV are used. First method is to measure Maximum Vertical Pocket (MVP) depth. It refers to the vertical dimension of the largest pocket of amniotic fluid not containing umbilical cord or fetal extremities and measured at a right angle in the uterine surface. Oligohydramnios is considered if the depth of MVP $< 2$ cm and Polyhydramnios is considered if the MVP depth is $\geq 8$ cm. The second method is to measure Amniotic Fluid Index (AFI). It is calculated by first dividing the surface markings of the uterus into four quadrants using the linea nigra and umbilicus. The maximum vertical amniotic fluid pocket diameter in each quadrant not containing cord or fetal extremities is measured in centimeters and then the sum of these measurements constitutes the AFI. Oligohydramnios is labeled when AFI is $\leq 5$ cm and Polyhydramnios is labeled when AFI $\geq 24$ cm. The assessment of AFV in twin pregnencies is especially important, given their high perinatal mortality rate. The MVP technique seems to be the most appropriate in twins, using the same definitions that are used in singletons. The use of the AFI in twins has poor inter-

and intra observer variability, and therefore should not be used in clinical practice[4,5,6].

Oligohydramnios, occur in 4% of all pregnancies and 12% of post-date pregnancies[1]. This may be evident in cases of leaking fluid from a tear in the amniotic membranes, measuring small in volume for a certain stage of pregnancy by ultrasonography or if the fetus is not moving as much as it would be expected to. It can also be occurs in mothers with a history of any of the medical conditions, like prior growth-restricted pregnancies, Hypertensive disorders in pregnancy, Problems with the placenta, (for example, abruption), Diabetic disorders in pregnancy, SLE and other autoimmune conditions, Multiple pregnancies (for example twins or triplets), Birth defects, such as kidney abnormalities, Delivering past the due date and other unknown reasons, known as idiopathic.[1,7,8]

According to the American Pregnancy Association, polyhydramnios can be occurs in 1% of all pregnancies[1]. Fetal disorders that can lead to polyhydramnios include gastrointestinal disorders (duodenal or esophageal atresia, gastroschisis, and diaphragmatic hernia), Brain or nervous system disorders (anencephaly or myotonic dystrophy), Achondroplasia, Fetal heart rate problems, Infection, Beckwith-Wiedemann syndrome, Fetal lung abnormalities, Hydrops fetalis, Twin-to-Twin Transfusion syndrome and Rh incompatibility or Kell diseases. Poorly controlled maternal diabetes also increases the risk. Too much fluid can also be produced during multiple pregnancies[3].

Polyhydramnios causes maternal symptoms like abdominal pain and difficulty breathing due to the enlargement of the uterus. Other complications include preterm labour, premature rupture of membranes, placental abruption, stillbirth, postpartum hemorrhage, fetal malposition, cord prolapsed[3].

Amniotic fluid volume disorders can happen during any trimester but is more evident during second and third trimesters. During that time, there is a higher risk for loss of pregnancy, preterm birth, or neonatal loss of life[4]. Associated birth defects are mostly the cause of abnormal amniotic fluid volume and also responsible for adverse perinatal outcome[3,9].

## II. Methods

A retrospective observational study was done in the Maternal-Fetal medicine (MFM) unit of Obs and Gynae Department, Dhaka Medical College Hospital, Bangladesh. After taking permission from hospital authority and Obgyn department, the patient's records from January to December 2020 were retrieved. Permission from Ethical review board was taken for publishing the data (Ref. Memo No. ERC – DMC/ECC/2021/422). From records of all admitted patients of MFM unit, the women who had abnormal amniotic fluid volume were sorted out. Two types of amniotic volume abnormalities were separated and analyzed. Oligohydramnios was defined when AFI is ≤ 5 cm and Polyhydramnios was defined when AFI ≥ 24 cm. in case of multiple pregnancy MVP measurement was considered along with AFI. Patient's anthropometric data, previous medical status and current pregnancy complications along with perinatal outcomes were put on SPSS (version 16). Analysis was done by using frequency and percentage for categorical data and mean±SD for quantitative variables. Data was presented as charts and diagrams for better understanding.

## III. Results

During the year of 2020 total 656 patients were admitted in Maternal-Fetal Medicine unit of Obs and Gynae department, Dhaka Medical College and Hospital, Bangladesh. Among them 130 (19.8%) patients were diagnosed as having oligohydramnios in their current pregnancy and 27(4.1%) patients were diagnosed as having polyhydramnios (Fig 1).

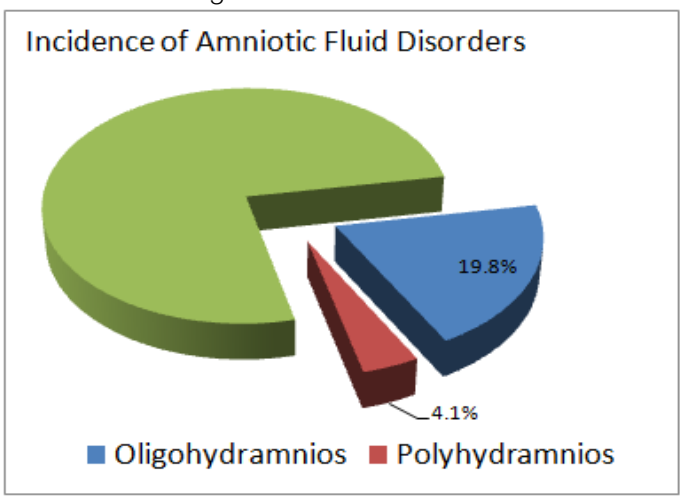


*Fig. 1:* Incidence of Amniotic Fluid Volume Abnormalities Among High Risk Patients

The mean age of our patients having oligohydramnios was 25.99±5.11 years and polyhydramnios were 24.71±4.39 years. All patients were of south-east Asian origin.

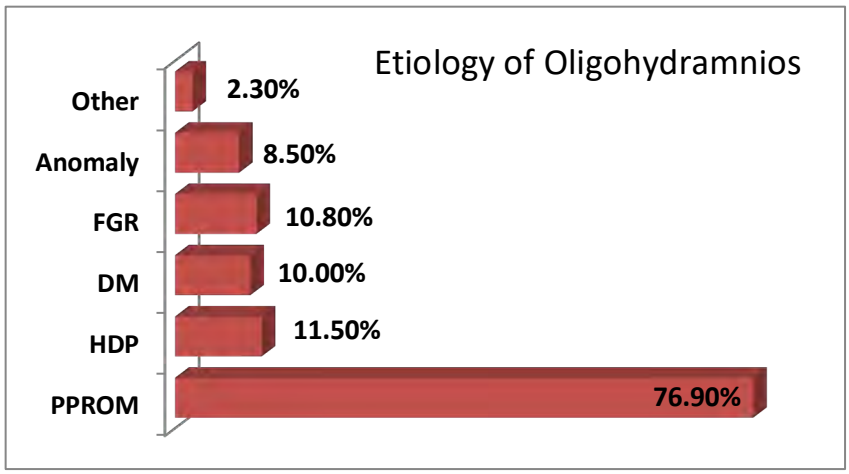


*Fig. 2:* Associated Problems with Oligohydramnios (There Were Some Overlapping Conditions So the Total Percentage was Not Exactly 100%)

Most of the oligohydramnios (76%) were due to preterm prelabor rupture of membrane. Other associated conditions of oligohydramnios were hypertensive disorders of pregnancy and growth restricted fetus (11.5%), Diabetic disorders (10.0%), Anomalous fetus (8.5%) and undetermined causes (2.3%).

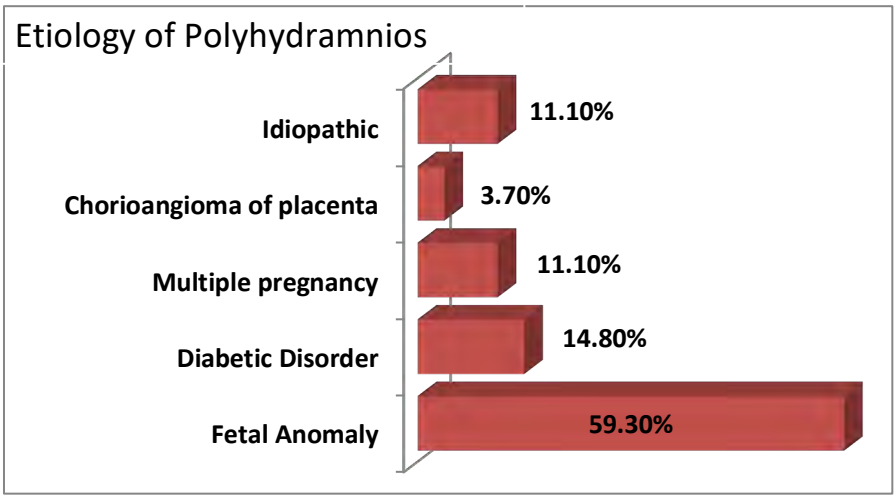


*Fig. 3:* Associated Problems with Polyhydramnios

Polyhydramnios was mainly associated with fetal anomaly (59.3%) but a little percentage was associated with gestational diabetes (14.8%), multiple pregnancies (11.1%), chorioangioma (3.7%) and undetermined (11.1%) causes.

Out of 130 oligohydramnios patients 83 were delivered in our hospital and the rest were taken discharge in undelivered state. The mean gestational age of delivery was 31.3± 2.73 weeks. Among them 63 (75.9%) babies were born alive and 20(24.1%) were still birth. 29 (34.93%) of the live babies needed admission in NICU and 9 (10.84%) of the admitted babies died during their neonatal period.

The total number of polyhydramnios patients 27 and 20 patients were delivered in our hospital. The mean gestational age of delivery was 32.0± 4.29 weeks. Among them 10 (50.00%) babies were born alive and 10 (50.00%) were still birth. 5 (25.00%) of the live babies needed admission in NICU and 4 (20.00%) of the admitted babies died during their neonatal period.

## IV. Discussion

Dhaka Medical College Hospital (DMCH) is the largest tertiary hospital of Bangladesh which is fully supported by government. High risk pregnancy patients came here from all over the country and got admitted in

Maternal Fetal medicine unit of Department of Obs and Gynae, for better management.

In this study the total number of admitted patient under Maternal Fetal Medicine unit of ObGyn department DMCH were 656 in the year 2020. Out of them 130 (19.8%) patients were diagnosed as having oligohydramnios and 27(4.1%) patients having polyhydramnios in their current pregnancy. Bakhsh et al found incidence of oligohydramnios 11.7% and polyhyhramnios 2.8% in a secondary care hospital of Saudi Arabia[6]. As our hospital is a tertiary center and the current study was conducted in a high risk pregnancy unit so incidences are higher in our study.

The mean age of our patients having oligohydramnios was 25.99±5.11 years and polyhydramnios were 24.71±4.39 years. All patients were of south-east Asian origin.

Most of the oligohydramnios (76%) were due to preterm prelabor rupture of membrane. Other associated conditions of oligohydramnios were hypertensive disorders of pregnancy and growth restricted fetus (11.5%), Diabetic disorders (10.0%), Anomalous fetus (8.5%) and undetermined causes (2.3%). Bakhsh et al showed 13.7% Diabetic Disorders, 5.2% fetal anomaly but no hypertensive disorders among oligohydramnios patient[6]. Lavanya B et al found 24% hyperhensive patients and 15% of growth restricted fetus with oligohydramnios[7]. The inclusion of prelabor rupture of membrane in our study may be the most influential factor for making etiological difference from other studies.

Polyhydramnios was mainly associated with fetal anomaly (59.3%) but a considerable percentage was associated with gestational diabetes (14.8%), multiple pregnancies (11.1%), chorioangioma (3.7%) and undetermined (11.1%) causes. Bakhsh et al showed 42.9% diabetic disorder, 7.1% hypertensive disorders, 14.2% fetal anomaly among polyhydramniotic patients[6]. Abele et al found 40% of the polyhydramnios cases as idiopathic[10]. The percent of idiopathic in our study was found less may be caused by advancement of investigation facilities.

Out of 130 oligohydramnios patients 83 were delivered in our hospital and the rest were taken discharge in undelivered state. The mean gestational age of delivery was 31.3± 2.73 weeks. Among them 63 (75.9%) babies were born alive and 20(24.1%) were still birth. 29 (34.93%) of the live babies needed admission in NICU and 9 (10.84%) of the admitted babies died during their neonatal period. Bakhsh et al showed 24.1% NICU admission of babies among oligohydramnios pregnancies[6]. Lavanya B et al found that 45% of baby needed NICU admission after delivery from an oligohydramniotic condition. Lavanya B et al also found 10% still birth and 2% neonatal death among patients with oligohydramnios[7]. So we have found a significant percent of hospital admission in all studies.

The total number of polyhydramnios patients 27 and 20 patients were delivered in our hospital. The mean gestational age of delivery was 32.0± 4.29 weeks. Among them 10 (50.00%) babies were born alive and 10 (50.00%) were still birth. 5 (25.00%) of the live babies needed admission in NICU and 4 (20.00%) of the admitted babies died during their neonatal period. Bakhsh et al showed 35.7% of babies from polyhydramnios pregnancy as NICU admission. So polyhydramnios is a major factor for adverse perinatal outcome. This may be due to the strong association of anomaly babies and diabetic mothers.

## V. Conclusion

To identify pregnancies with risk of poor perinatal outcomes, AFI measurement can be used as one of the important method. Ultrasound evaluation of abnormal amniotic fluid volume indicates a wide range of pregnancy complications and can predict adverse perinatal outcome for that pregnancies.

*Recommendations for future research:*

- To conduct large study in a more precise way so that the rare etiologies come in front.
- Long term outcome of babies should be followed to evaluate the consequences.

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*All Subspecialty trainee of Maternal Fetal Medicine, Dhaka Medical College Hospital.

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# Uterine Fibroids. What We Know and What We Need to Know

By Maria O. Korchagina& Irina S. Grigoryan
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*Abstract-* Uterine fibroids (UFs) are the most common tumours of the female reproductive system and represent a significant health issue worldwide. UFs develop during reproductive span and often shrink after menopause.UFs affect over 70% of women by the onset of menopause. Uterine fibroids arise from myometrial smooth muscle cells. UFs can be solitary or multiply and their size varies from microscopic to giant. Nowadays the exact cause of UFs remains unknown, but it is assumed that genetic abberations along with steroid hormones and growth factors play a pivotal role in thetumour development. In most cases UFs are asymptomaticand therefore it is difficult to estimate their actual prevalence. Symptomatic UFs present with abnormal menstrual bleeding, pelvic and low back pain, bulk symptoms, infertility and have a strong impact on health-related-quality-of-life (HRQL). Early diagnosisand treatment of UFs as well as preventive measures, especially for patients from high-risk groups, should be a priority.

This article presents current data about pathophysiology, diagnosisandmanagement of UFs.

*Keywords: leiomyoma, myometrium, estrogens, progesterone, growth factors, menopause, fertility, uterine myomectomy, hysterectomy.*

*GJMR-E Classification: DDC Code: 618.175 LCC Code: RG186*


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# Uterine Fibroids. What We Know and What We Need to Know

Maria O. Korchagina [α] & Irina S. Grigoryan [σ]

*Abstract-* Uterine fibroids (UFs) are the most common tumours of the female reproductive system and represent a significant health issue worldwide. UFs develop during reproductive span and often shrink after menopause. UFs affect over 70% of women by the onset of menopause. Uterine fibroids arise from myometrial smooth muscle cells. UFs can be solitary or multiply and their size varies from microscopic to giant. Nowadays the exact cause of UFs remains unknown, but it is assumed that genetic abberations along with steroid hormones and growth factors play a pivotal role in the tumour development. In most cases UFs are asymptomaticand therefore it is difficult to estimate their actual prevalence. Symptomatic UFs present with abnormal menstrual bleeding, pelvic and low back pain, bulk symptoms, infertility and have a strong impact on health-related-quality-of-life (HRQL). Early diagnosis and treatment of UFs as well as preventive measures, especially for patients from high-risk groups, should be a priority.

This article presents current data about pathophysiology, diagnosis andmanagement of UFs.

*Keywords: leiomyoma, myometrium, estrogens, progesterone, growth factors, menopause, fertility, uterine myomectomy, hysterectomy.*

## I. Introduction

Uterine fibroids (UFs), also known as leiomyoma or fibroids, are benign monoclonal tumours originating in smooth muscle cells of the cervix or uterine corpus. UFs are the most common pelvic benign tumour of the female reproductive system, occurring in 20-40% of reproductive-age women, >40% of women over the age of 40 years and >70% of women by age 50 [1,2]. The average age of detection of UFs is 32-34 years, and highest incidence is at the onset of menopause [3]. There is an increasing incidence of UFs in young women under 30 years of age who have not fulfilled their reproductive function.

## II. Etiology and Pathogenesis of Uterine Fibroids

As is well known, the myometrium, the middle layer of the uterine wall, is the thickest tissue of the uterus and composed of longitudinal and circular layers. The myometrium is located between serous or peritoneal layer and mucosal layer called endometrium and consists not only smooth muscle fibres but also blood and lymph vessels and nerves.

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As previously stated, UFs have a clonal origin with proliferation of smooth muscle cells and fibroblasts [4]. Uterine fibroids develop from one primary mutant cell of smooth muscular tissue of myometrium, which acquires the ability to grow unregulated. Therefore “fibroid” is not accurate term for describing this tumour, because it does not arise from fibrous tissue, but it contains a large amount of extracellular matrix, including fibrillar component (collagen, elastin) and interfibrillar component (fibronectin, proteoglycans), and is surrounded by a thin pseudo-capsule. In UFs, ECM is composed mainly of collagen types I and III and mRNAs for *COL1A1*, *COL1A2*, *COL3A1*, *COL5A1*, *COL5A2*, and *COL7A1*are up-regulated compared with normal myometrium. One of the mechanisms underlying the excessive accumulation of ECM in UFs is the down-regulation of miR-29b [5].

Visually, uterine fibroids present as round, hard, white or pale pink neoplasms composed of smooth muscle with varying amounts of fibrous connective tissue. If UFs are not microscopic and/or growing, they can significantly distort the surface of the uterus or its cavity.

The pathogenesis of UFs growth is highly complex. There are many factors that influence the development of uterine fibroids, but the changes in signalling pathways are crucial in cell proliferation. The most significant causes of UFs development are discussed below.

### *a) Genetic Changes*

Genetic changes contribute to an increased proliferative or decreased apoptotic index and may be associated with UFs in approximately 90% of cases [6]. Genetic alterations in High Mobility Group AT-Hook 1 (*HMGA1*) and High Mobility Group AT-Hook 2 (*HMGA2*) genes and somatic mutations in Mediator Complex Subunit 12 *(MED12)* gene, particularly in exon-2 region, are the most significant in UFsdevelopment [7, 8, 9, 10]. *MED12* and *HMGA2* mutations are independent genetic events in UFs [11]. It has been shown that mutations in *MED12* and overexpression of *HMGA2* mRNA can be detected simultaneously in UFs [12]. Another genetic mutations *FH*, *COL4A5*/*A6* and the unknown ones may be responsible for UFs without changes in *HMGA2* and *MED12* [11].

i. *HMGA Family Member*

*HMGA1* (6p21) and *HMGA2* (12q14–15) are a protein coding genes, influencing cell cycle kinetics [13]. These genes are involved in many cellular processesand participate in alteration of chromatin structure and activation of transcription. *HMGA1* encodes non-histone chromatin-associated proteins HMGA1a, HMGA1b andHMGA1c and*HMGA2* encodes non-histone chromosomal protein HMGA2.

The main role of proteins encoded by *HMGA1*are regulation of gene transcription, DNA repair, heterochromatin organization, cell (including stem cell) differentiation and proliferation [14]. *HMGA2* overexpression is the second most common genetic change in UFs, identified in 7.5–10% of cases. It also acts as a transcriptional regulator. HMGA proteins are often expressed at very high levels in benign tumors (lipomas, uterine leiomyomas, breast fibroadenomas, salivary gland adenomas, pituitary adenomas), where in most cases, chromosome rearrangements involving the *HMGA2* gene, but also *HMGA1* gene [15]. HMGA proteins are expressed at high levels during embryogenesis. Overexpression of HMGA lead to inducing neoplastic transformation and promote of metastatic progression therefore it can be considered that HMGA proteins influence cell growth [16].

*HMGA2* probably influence activity of fibroblast growth factor pathway and lead to UFs growth. According to a study by Helmke BM and et al, UFs with rearrangements of the *HMGA2* were found to express significantly higher levels of *FGF2* than those with an apparently normal karyotype. In addition, there was a linear relationship between the expression of *FGF2* and the level of *HMGA2* overexpression and the size of UFs. [17]. The overexpression of *HMGA1* and *HMGA2* mRNA may lead to upregulation of angiogenesis [18].

ii. *MED12*

Transcription initiation is known to be partially controlled by the preinitiation complex (PIC). It includes a transcriptional coactivator complex called Mediator. Together with general transcription factors, Mediator stimulates PIC formation and activates RNA polymerase II (Pol II) transcription. The product of the *MED12* gene, MED12 protein, is part of the CDK8 subcomplex along with MED13, CDK8 and cyclin C and is required for activation of CDK8 kinase. The CDK8 subcomplex binds to the mediator and modulates the interaction of Mediator with Pol II.

Somatic mutations in *MED12*, especially in exon 2, are proposed to be one of the underlying cause of UFs. *MED12* gene is mutated in 70-75% of tumours [11, 19]. *MED12* plays an important role in regulating genes such as *WNT*, *CCND1*, *AXIN2*, and *MYC*, which pertinent to cell cycling and cell proliferation MED12 somatic mutation has the potentials for myometrial cell transformation by dysregulating oncogenic Wnt4/β-catenin signaling. In the study of El Andaloussi A and co-authors have been showed that cells with common *MED12* somatic mutation has increased levels of protein expression of Wnt4 and β-catenin, mTOR protein and oncogenic cyclin D1 which might lead to inhibition of autophagy, increase of cell proliferation and UFs development [20].

*b) Steroids*

There are estrogen receptors (ER) and progesterone receptors (PR) in myometrium. It is known that UFs contain ER and PR in higher concentrations. The relative expression levels of ER and PR are upregulated in UFs compared to the surrounding myometrium. Estrogens and progesterone (P4) act as stimulators of UFs growth, the effects of these steroid hormones in the development of UFs are complementary.

UFs cells are known to have increased levels of aromatase and 17-hydroxysteroid dehydrogenase, enzymes that contribute to estradiol production. Increased exposure to circulating oestrogen may contribute to tumour growth by increasing extracellular matrix production.

i. *Estogens*

Estrogens are one of the main hormones produced by the ovaries and responsible for the development and regulation of the female reproductive system. Their action is mediated by ER. There are two best studied isoforms of ER – ERα and ERß. Estradiol (E2), the most potent form of estrogen steroid hormone, enters the cell and binds to ER. Formed hormone-receptor complex translocates to the nucleus and binds to a specific DNA site, leading to activation of gene expression, synthesis of specific proteins and promotion of hormonal effects.

E2 acts mainly through the ERa. It induces the transcription of genes involved in proliferation, but its one of the main functions leading to growth of UFs is to increase myometrium tissue sensitivity to progesterone via induction of PR expression.

Conventionally, estrogens has been considered the major factor for UFs development. Estrogens are involved in activation of fibroblasts, which may play key role in proliferation of UFs cell. The expression levels of ER is known to be higher in cells of UFs than in surrounder miometrium. According to Luo N. and et al, fibroblasts are activated in UFs, and estrogen may stimulate fibroblast activation, increase their proliferative activity, and increase the expression of fibroblast activation protein (FAP), growth factors such as transforming growth factor-β (TGFβ), insulin-like growth factor-1 (IGF-1) and ECM components. Silencing of FAP expression can inhibit the effect of estrogen on tumour-associated fibroblasts (TAF), thus FAP plays an important role in oestrogen-mediated fibroblast

activation. To sum up, estrogen may promote UFs cell proliferation through fibroblast activation [21].

ii. *Progesterone*

It is now believed that, progesterone is the main hormone that stimulates the growth of UFs. UFs growth significantly in postmenopausal women who receive hormone replacement therapy with combined estrogen and progesterone, and not with estrogen replacement therapy. In Ishikawa H and et al study an animal xenograft model was used to elucidate the functions of ovarian steroids. It was found that treatment with estradiol alone did not increase or maintain the size of UFs [22].

The responses of progesterone are mediated by non-genomic pathway and genomic pathway [23]. The majority of the effects of progesterone in the human organism are mediated by PR. PR is a member of the steroid-receptor superfamily of nuclear receptors. There are two isoforms of PR, PR-A and PR-B, which produced from a single gene by translation initiation at two distinct start codons [24]. PR-A is a truncated form of PR-B. PR-A and PR-B vary in their transcriptional activity. PR-B acts as a potent activator of transcription of target genes and PR-A acts as a repressor of transcription of PR-B [25]. When progesterone binds to PR, a ligand-receptor complex is formed. This complex translocates to the nucleus, binds to DNA and activates the expression of specific target genes.

The ratio of PR-A to PR-B in specific tissues defines the responses to progesterone. There is increased expression of both PR-A and PR-B in UFs. Estradiol (E2) is an important inducer of RP expression supported progesterone action. According to Ishikawa H et al., progesterone is essential for maintenance and growth of uterine leiomyoma. E2 enhances the synthesis of ER, PR and androgen receptors. Progesterone, on the contrary, inhibits the synthesis of ER and PR.

During the secretory phase, when levels of progesterone are at their highest, proliferation markers and the count of mitoses are also highest in UFs tissues. Progesterone activates the AKT pathway and its effectors, glycogen synthase kinase-3b (GSK3b) and Forkhead box O-1 (FOXO1), leading to UFs cells proliferation and promotion their survival [26]. P4 also stimulates EGF, Bcl-2 expression and inhibites TNF-α expression in the cells, which lead to growth and survival of UFs cells [27].

One of the causes of UFs is the inhibition of mechanisms of apoptosis. There are influence of progesterone on the regulation of apoptosis in the myometrium. In Omar M and et al studies demonstrated that five progesterone-regulated genes (PRGs), playing crucial roles in cell proliferation, apoptosis, tumorigenesis, reorganization and renovation of tissues, such as *Bcl2*, *FOXO1A*, *SCGB2A2*, *CYP26a1* and *MMP11* exhibited significant progesterone-hyper-responsiveness in UFs cells compared to normal myometrial cells. Seven PRGs such as *CIDEC*, *CANP6*, *ADHL5*, *ALDHA1*, *MT1E*, *KIK6*, *HHI* showed increase repression in the case of progesterone treatment [28].

It is assumed that progesterone-dependent UFs growth requires a population of stem/progenitor cells. It has a reduced expression of ERα and PR, and depends on high levels of ERα and PR in the surrounding mature myometrium. Progesterone sends paracrine signals via activation of the WNT/β-catenin pathway from mature cells to stem cells [29].

c) *Others*

There are *tissue-specific stem cells* (SSC) in the myometrium. They allows uterus to regenerate and remodelate, which is particularly important during pregnancy [30]. Due to the presence of stem cells within the UFs, the tumour is able to reconstitute itself [31].

*The growth factors* such as epidermal growth factor (EGF), insulin-like growth factor (IGF), transforming growth factor-b (TGF-b), platelet-derived growth factor (PDGF) have a stimulating effect on UFs cell proliferation. Vascular endothelial growth factor (VEGF), tumour necrosis factor α (TNF-α), haematopoietic growth factors (HGFs) may be also involved in pathogenesis [18,32]. Growth factors act as the ultimate effectors of steroid hormones. Estradiol and progesterone regulate the expression levels of various growth factors in the myometrium. E2 stimulates EGF receptor (EGF-R) expression and P4 stimulates EGF expression in UFs cells [33].

Myostatin (MSTN) and activin A are the members of the TGF beta protein family. Myostatin and activin act as inhibitor of muscle cell growth. Their signalling is regulated by membrane and extracellular factors, including activin-binding proteins such as follistatin and follistatin-related gene (FLRG). Follistatin may inhibit the activity of MSTN and activin [34]. According to Lee SJ and et al, the higher expression of follistatin, FLRG and Cripto in UFs produce reduced sensitivity to the anti-proliferative effects of myostatin and activin on myometrial cells and therefore lead to UFs development [35].

*The phosphatidylinositol 3-kinase (PI3K)/AKT/ mammalian target of rapamycin (mTOR) pathway* is an intracellular signaling pathway involved in regulation of cellular functions such as metabolism, proliferation. The PI3K/AKT/mTOR signalling pathway is involved in the initiation and regulation of autophagy, but also play a key role in carcinogenesis. UFs growth is also associated with activation of the PI3K/AKT–mTORpathway. The PI3K/AKT/mTOR pathway contribute to tumor growth by stimulation of proliferation, invasion, metastasis and survival of tumour cells. Another signaling pathway playing a significant role in pathogenesis of UFs is Ras/Raf/MEK/ERK pathway [36].

*Chronic inflammation* characterised by the formation of new blood vessels, increased vascular permeability, proliferation of fibroblasts and other events may cause the development of UFs. Cytokines such as tumor necrosis factor-α, erythropoietin, interleukin-1, interleukin-6 as well as several chemokines and their receptors may implicated in development of UFs. Inflammatory cells which may contribute to excessive production of ECM as well as tissue remodeling have been found in UFs [37].

Epigenetic changes and microRNAs (miRNAs) may be involved in pathophysiology of UFs**.** It became known that the expression profile of miRNAs in UFs cells differed from that in normal myometrial cells. The relative expression level of miR-15b was upregulated, and the relative expression levels of miR-29a, -29b, -29c, -197, and -200c were downregulated in UFs. Moreover, the miRNA expression profile in UFs cells differed according to their ability to lead to UFs with endometrial cavity distortion. The expression profile of miRNAs in UFs may effect on occurrence or absence of endometrial cavity distortion [38].

According to the study of, vasculogenesis and angiogenesis may play significant role in UFs formation, which in turn may be part of a vascular disease process [18].

## III. Types of Uterine Fibroids

The size and location of the tumour may influence the onset of symptoms, the need for treatment and the method of treatment. There are three main types and other rare types of fibroids depending on its location in the uterus. The universally accepted International Federation of Gynaecology and Obstetrics (FIGO) classification system (PALM-COEIN) for causes of abnormal uterine bleeding includes leiomyoma subclassification system. This system includes the submucosal, intramural, subserosal, transmural and other lesions (Fig. 1).

- Subserosal fibroidsgrow out toward the serosal surface of the uterus covered by peritoneum. They may be sessile, pedunculated (attached to the surface by a stalk) or intraligamentary (between the two peritoneal layers of the broad ligament).
- Intramural fibroids are the most common type and located within the myometrium separated from the surrounding tissues by pseudo-capsule. They may lead to distortion of the uterine cavity and its surface.
- Submucosal fibroids grow toward the endometrium, protruding into the uterine cavity.
- Cervical fibroids are located in the cervix. They are a rare type.

| | | |
|---|---|---|
| **Submucosal** | 0 | Pedunculated intracavity |
| | 1 | ≤ 50% intramural |
| | 2 | > 50% intramural |
| **Other** | 3 | 100% Intramural but contains endometrium |
| | 4 | 100% Intramural |
| | 5 | Subserosal, ≥ 50% intramural |
| | 6 | Subserosal, < 50% intramural |
| | 7 | Subserosal pedunculated |
| | 8 | Other (cervical, parasitic) |
| **Hybrid** *(impact both endometrium and serosa)* | 2-5 | Submucosal and subserosal |

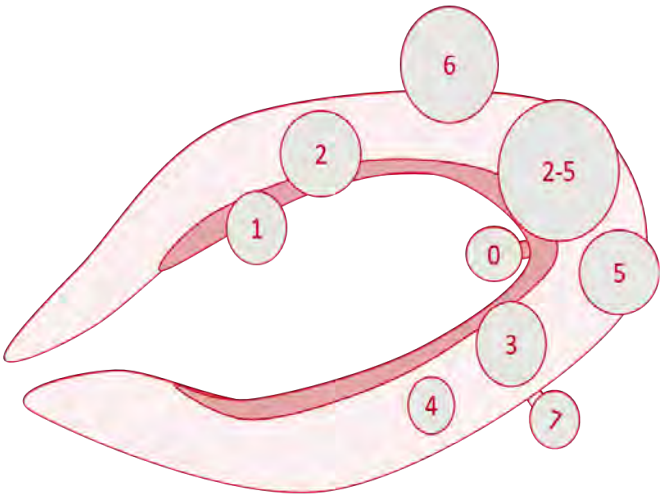


*Figure 2:* FIGO Classification of Uterine Fibroids According to Munro et al. (2011).

The FIGO classification of fibroids has clinical limitation. In the paper and co-authors showed that the FIGO classification of fibroids was not consistent between two gynaecologists and two radiologists specializing in UFs. Variations were clinically relevant (influencing surgical planning) for 36% of the fibroids [39]. Therefore, additional validation of the FIGO classification system for fibroids is required.

## IV. Risk Factors

There are many risk factors associated with the development of uterine fibroids [3, 40]:

- Age – women aged 41-50 or 51-60 years are 10 times more likely to have myoma than those aged 21-30 years.

- Positive family history – in patients with positive family history, the risk for developing UFs approximately three-four times higher than in the general population.
- African American race – black women were found to have a two–threefold greater risk of developing UFs than white women. African-American women have more severe symptoms.
- Compared to white women.
- Early menarche (less than 11 years) – patients with an early age at menarche have a greater lifetime exposure of the myometrium to oestrogens.
- Absence of childbirth (nulliparity) vs high parity (≥3) – parity is associated with a reduced risk of developing UFs.
- Time since last birth – the risk of developing UFs is increased in women who last gave birth 5 or more years ago compared with those who gave birth more recently.
- Obesity – an increased risk of UFs is associated with higher oestrogen levels in obese women because adipose tissue is a source of oestrogen.
- Premenopausal state – three to five times higher risk than in postmenopausal women.
- High blood pressure (hypertension).

The role of smoking as one of the protective factors of UFs is discussed. In one study, smoking was found to reduce UFs risk, but only in the case of patients with a low BMI (≤22.2 kg/m$^2$). The use of food additive increases the risk of UFs. The intake of soybean products (eg milk) has been identified as risk factor for their endocrine-disrupting chemical (EDC) contain such as genistein. According to some studies, the use of oral contraceptives, injectable contraceptive (depot-medroxyprogesterone acetate) as well as reproductive characteristics such as later age at menarche, longer menstrual cycles and breastfeeding were found to reduce the risk of developing UFs and may be reproductive protective factors [41, 42].

Another potential risk factors may include intake of caffeine and alcohol, several reproductive characteristics (shorter menstrual cycles, late reproductive age), cervical neoplasia, pelvic inflammatory disease, chlamydial infection, use of perineal talc, diabetes mellitus, polycystic ovary syndrome, metabolic syndrome [43,44]. UFs may be associated with cardiometabolic risk factors and atherosclerosis [45].

## V. Symptoms and Signs of Uterine Fibroids

According to various sources, symptoms are found in about 35–50% of patients. Important to understand that quality of life (QoL) depends directly on the severity of UF-associated symptoms.

*Signs and symptoms of UFs include:* heavy menstrual bleeding leading to anaemia; painful periods; pelvic non-cyclic pain; pelvic pressure; lower back pain; dyspareunia; bowel or bladder dysfunction [46].

UFs can be accompanied by sub fertility, pregnancy complications, spontaneous abortion, ectopic pregnancy or such obstetric outcomesas obstructed labour, cesarean delivery, fetal malpresentation, placenta previa due to interference with implantation of the ovum in the upper uterine segment, placental abruption, premature rupture of membranes, premature or threatening premature delivery, postpartum haemorrhage and aseptic necrobiosis of a uterine fibroid during pregnancy [47, 48].

## VI. Diagnosis of Uterine Fibroids

The diagnosis of uterine fibroids is made on the basis of signs and symptoms, physical and instrumental examinations and laboratory tests.

*a) Physical Examination*

This stage of diagnosis may help to identify uterine fibroids as well as their localization. Uterine size is described in weeks (as that of a pregnant uterus). UFs may discovered by pelvic examination as a firm mass of an irregular shape on the uterus or as enlarged and irregular uterus. In the case of cervical UFs localization the cervix is smooth, asymmetrically positioned, displaced to the opposite pelvic wall.

*b) Instrumental Examinations*

The next step is doing one or more of different types of imaging techniques to confirm the diagnosis and identify the location, shape, size, number of fibroids and their types.

Pelvic ultrasound with using transabdominal and transvaginal transducer is non-invasive technique which recommended as the main screening and primary diagnosis of uterine myoma. Ultrasound allows to exam the uterus and the surrounding structures. This imaging technique provides an opportunity for topical diagnosis of UFs, their structure, hemodynamics, the severity of proliferative processes and detection of secondary changes in the nodes as a result of impaired blood circulation. It is also useful for differential diagnosis. On pelvic ultrasoundUFs are identified as a hypoechoic, well-circumscribed and round mass. Transvaginal ultrasonography is about 90% to 99% sensitive for detecting uterine fibroids.

The other types of imaging technology are: saline infusion sonography (sonohysterography), magnetic resonance imaging (MRI), hysteroscopy. Saline infusion sonography improves sensitivity for detecting fibroids. If ultrasound and sonohysterography are inconclusive, MRI is the most accurate imaging technology. MRI allows to detect the number and size of

fibroids, the degree of vascularisation, the location, boundaries with normal myometrium and relationship with the endometrial cavity and serosal surface, and, based on this, the type of UFs. UFs are well-defined masses and typically T2-hypointense compared to the normal myometrium and of intermediate signal intensity on T1-weighted images [49]. MRI is recommended for differential diagnosis with adenomyosis and for choosing the volume and access of reconstructive operation for patients with co-morbidities, large uterine fibroids sizes and also for patients planning to realize reproductive function and who have compression of adjacent organs.

Hysteroscopy is recommended in the case of suspicion of submucous localization of UFs, in order to exclude intrauterine pathology and for choosing the access to operative treatment.

*c) Laboratory Tests*

Examinations of the complete blood count, biochemical blood test, haemostasiogram are helpful in detecting complications (anaemia, impaired blood circulation in the node, etc.), in pre-operative examinations and in determining the treatment strategy.

## VII. Management of Uterine Fibroids

In the case of patients with asymptomatic UFs, there's no treatment needed. Patients should see a gynecologist and undergo routine pelvic ultrasound once every 6 to 12 months.

In the case of symptomatic UFs, the most appropriate treatment strategy, depending on anamnesis, patient's age and future fertility desires, is recommended.

*a) Medical Therapy*

Medical therapy must be effective, safe, accessible and well tolerated. It should be evaluated every 3 months and if it is not effective, other treatment should be prescribed. Based on the pathogenesis, the main target of the current medical therapy is focused on control of estradiol and progesterone production or their action. The main aim of medical treatment is to alleviate or eliminate the symptoms associated with UFs, and to reduce the size of fibroids [50].

Nowadays, there are at least two options for medical therapy, which effectively reduce both fibroid size and bleeding and it is Gonadotropin-releasing hormone (GnRH) analogues (agonists) and selective progesterone receptor modulators (SPRMs).

i. *GnRH Agonists*

GnRH agonists turn off synthesis of estrogen and progesterone and thus suppress ovulation.GnRH agonists lead to hypogonadotropic hypogonadal state, hypoestrogenism and temporary menopause (pseudomenopause). These effects develop after 1-3 weeks of drug administration [51]. GnRH agonists include leuprolide, triptorelin and goserelin. Benefits of GnRH agonists use include decrease in fibroid size, reduction of endometrial thickness and vascularization, reductions in uterine volume and resolution of anemia by restore hemoglobin levels.

GnRH agonists may use as presurgical adjuncts to make surgery easier or improve operative technique. In addition to the effects described above, GnRH agonists reduce intraoperative estimated blood loss, fluid absorption, rate of vertical incisions and decrease operative time [52,53,54]. The duration of pre-operative GnRH agonists therapy is 3 months. The duration of medical therapy with GnRH agonists is limited to 6 months due to side effects, which mayinclude menopause-like symptoms such as hot flashes, fatigue, decreased concentration, insomnia, emotional lability, vaginal drynessand decreased bone mineral density [55]. GnRH antagonists cannot fully contribute to relief from tumor, and after stopping treatment UFs may grow back along with return of symptoms.

Add-back therapy with GnRH agonists may include estriol, tibolone, raloxifene and ipriflavone which help to preserve bone density. Also intake of medroxyprogesterone acetate (MPA) and tibolone may reduce vasomotor symptoms [56,57].

ii. *SPRMs for Uterine Fibroids*

With the knowledge of the significant role of progesterone in the pathogenesis of UFs, selective progesterone receptor modulators (SPRMs) have been developed. SPRMs are a new class of drugs, which target PR and exert an agonistic and antagonistic effects [58]. Tissue and cell type influence SPRM activity and the effect of SPRM is more influenced by the ratio of co-activators to corepressors [59]. SPRMs include mifepristone, ulipristalacetate (UPA), telapristone acetate, onapristone, asoprisnil.

SPRMs have been shown efficacy and safetyin reducing the size of UFs, inducing amenorrhea and improving main symptoms and quality of life. The most widely discussed SPRMs is ulipristal acetate (UPA) [51]. UPAis tissue-selective synthetic steroid which reduce the proliferation of UFs cells and induces apoptosis [60]. It has been demonstrated that administration UPA reduces fibroid size, controls uterine bleeding and improves QOL [61,62,63]. In contract to GnRH agonists, UPA has a sustained effect (up to 6 months) on UFs size. According to several studies, UPA is well tolerated treatment option with less than 5% of cases with discontinuing treatment due to side effects [64,65].

In the end, SPRMs may be effective treatment for women with symptomatic (moderate and severe symptoms) fibroids, for preoperative use and for intermittent long-term treatment, but there are needs to well-designed RCTs comparing efficacy, cost-

effectiveness and safety of SPRMs and other treatment options in UFs therapy.

*b) Preoperative Adjuvant Therapy: SPRMs vs GnRH Agonists Leuprolide*

Women receiving UPA have significantly less faced with hot flashes and achieved amenorrhoea 2 weeks earlier than women receiving leuprolide [63,66]. UPA is more effective and well-tolerated option for the preoperative therapy.

Another medical options may include aromatase inhibitors and selective estrogen receptor modulators (SERMs). The first one modulate estrogen signaling pathway and the second one act differently in various tissues by blocking or stimulate estrogen-like action. Unfortunately their effectiveness is controversial [67,68].

*c) Surgical Treatment*

The evidences for surgical treatment of UFs are menstrual abnormalities leading to iron deficiency anemia; bulk symptoms (pressure symptoms); large tumour size (over 12 weeks gestation); rapid tumour growth (more than 4 weeks within 1 year); tumour growth in postmenopause; submucosal, interligamentary or cervical location of nodes; reproductive disorders (pregnancy failure, infertility in the absence of other causes); signs of circulatory disturbances in UFs [69,70].

Surgical treatment of UFs is performed during the 1st phase of the menstrual cycle (day 5-14) in a planned manner. When choosing the best surgical technique, the size and number of fibroids, their location, surgical history, age of the patient and the patient's preferences (e.g. preserve the uterus and fertility or not) should be considered. Other surgical approaches include hysteroscopic myomectomy, laparoscopic myomectomy or laparoscopic hysterectomy.

Myomectomy is the standard of care for women with symptomatic fibroids who wish to preserve fertility, but can be detrimental on pregnancy outcome [71].

i. *Hysteroscopic Myomectomy*

Hysteroscopic myomectomy is the standard minimally invasive surgical procedure in the treatment of submucosal UFs (especially, Figo type 1-2). Most commonly, hysteroscopic myomectomy is performed in two steps: under hysteroscopic control, the protruding part of fibroid is resected or ablated; the remaining intramural component rapidly migrates into the uterine cavity, allowing complete and safe excision of the myoma during the second step.

ii. *Laparoscopic Myomectomy*

Laparoscopic myomectomy (LM) is the gold standard in the treatment of women of reproductive age. However, it is worth noting that there is a significant risk of uterine rupture during pregnancy or delivery, and this is primarily due to the inability to adequately match the wound margins during LM (especially type 3-5 and type 2 with an intramural component of more than 20%) and the use of electrosurgical devices (tissue burn and disruption of its regeneration). Also note that it is recommended to use morcellator in a special container (endobag) to avoid dissemination. Currently, the ideal condition for LM is UFs type 7.

a. *Minilaparotomy as Analogue of LM*

Minilaparotomy implies an extra special incision in the abdominal wall with an extension of the umbilical puncture to 3-5 cm. Minilaparotomy myomectomy is a minimally invasive surgical intervention that allows the surgeon to maintain tactile contact with the uterus and close the myometrial defect after fibroids enucleation easily. Minilaparotomy myomectomy becomes a good solution in the case of limited laparoscopic suturing skills and may provide better uterine reconstruction in the case of large fibroids [72]. Another advantages of minilaparotomy is a faster removal of UFs from the cavity and reduction in the time of myomectomy [73].

b. *Benefits of LM*

LM was associated with longer operative time but fewer general complications, lower blood loss, lower decline in haemoglobin concentrations and less postoperative pain (on avisual analogue scale) and a faster recovery after surgery compared with abdominal (open) myomectomy [74,75,76].

iii. *Hysterectomy*

Hysterectomy is performed in patients with symptomatic UFs who not planning pregnancy or in the case of post-menopausal women. Access (laparoscopy, laparotomy, transvaginal) and the extent of surgical intervention (subtotal without or with uterine adnexa, total hysterectomy or panhysterectomy) depend on the patient's age, the size of the uterus and UFs, the presence of concomitant pathologies of the cervix or uterine adnexa, the surgeon's qualifications and the patient's preference.

Other ways to perform myomectomy include robotic assisted laparoscopic myomectomy, laparoscopic-assisted minilaparotomy (LA-MLT), single-port laparoscopically assisted-transumbilical ultraminilaparotomic myomectomy (SPLA-TUM), single port laparoscopic myomectomy (SP-LM) [77-81].

*d) Alternative Treatment*

i. *Uterine Artery Embolization*

Uterine artery embolization (UAE) was originally introduced in 1995 [82]. Nowadays, UAE is a well-established safe and minimally invasive treatment for UFs which provides good symptom relief. UAE should be considered as one of the treatment options as well as the conventional surgical treatments. It may apply in the case of patients at high surgical riskor for patient with increased risks of complications of general

anesthesia, as an alternative to surgical treatment; for those patients, who categorically reject surgical or hormonal treatment. It should be noted that UAE use remains controversial for women who wish to procreate, because the procedure can affect fertility and the course of pregnancy.

Before the UAE, accurate pre-treatment diagnosis with MRI is recommended. UAE is performed by interventional radiologist with specialised experience in embolization. Through a small incision in the groin, the radiologist set a catheter into femoral artery, after the catheter is threaded into uterine artery, the blood vessel that supply the uterus. Under X-ray control small spherical particles of medical material are delivered through the catheter to form a blockade to the blood. UAE induces ischemic necrosis of UFs, while normal myometrial tissue revascularizes, that is to say, UAE leads to devascularization of UFs without affecting healthy uterus tissue. The majority of UFs have a limited supply by the uterine arteries, thus after UAE they are impacted simultaneously. Deprived of nutrition, UFs become smaller for the three to six months following UAE.

The early and medium-term results of UAE are promising. Particularly it is effective for abnormal menstrual bleeding. The randomised controlled trials (RCTs) of UAE versus any surgical therapy for symptomatic uterine fibroids included in review by Gupta and et al. compared UAE with surgery. OAE, as well as surgery, was shown to improve quality of life, but with reduced the length of the procedure, decreased the likelihood of needing a blood transfusion, length of hospital stay and time to resumption of routine activities, however UAE was associated with higher rates of minor complications (e.g. puncture site bruising and self-limiting vaginal discharge in 20-30% of patients). No significant difference was found between UAE and surgery in terms of patient satisfaction [83].

Although UAE is highly effective in treating symptomatic UFs, there is risk of surgical reintervention within two to five years of the initial procedure. As reported by Gupta and et al., 7% of women will require further surgery within two years of hysterectomy or myomectomy, between 15% and 32% will require further surgery within two years of UAE [84].

UAE may apply as preparation for surgery. It decrease both uterine and UFs volume, reduces intraoperative bleeding and increases the possibility of uterus preservation [85].

There are differing opinions about the effectiveness of this technique. It is important to identify what determines the success of UAE. UAE has been reported to provide a good success rate in women with a single symptomatic intramural myoma and can be considered as an effective alternative procedure for UFs treatment [86]. Patient selection and counselling is of paramount importance due to the high risk of the need for further surgery.

There are a number of contraindications to UAE. For example, it is contraindicated if there is evidence of a current or recent infection and if there is significant doubt about the diagnosis of a benign pathology.

Patient selection and counselling is of paramount importance due to the high risk of the need for further surgical intervention, and especially in the case of patients of childbearing age who wish to become pregnant. The authors are divided on the use of UAE in women of reproductive age [87]. This is largely due to the fact that the exact effects of UAE on fertility are unclear. The increased risk of caesarean section and the possibility of increased pregnancy complications such as abnormalities of placental implantation, spontaneous abortion, premature delivery after UAE should be stipulated as well asholding pre-treatment fertility assessment [87]. Obviously, well-designed RCTs are needed to assess the impact of UAE on fertility and to subsequently compare the results of UAE with myomectomy. Recent research in the field has questioned the appropriateness of UAE as the main treatment for women wishing to give birth. UAE may be alternative in the case of patients of childbearing age not eligible for myomectomy According to Serres-Cousine O and et al, restoration of uterine anatomy and protection of the ovaries may be the main predictive factors for obstetric success, reducing the risk of miscarriage, and the main predictive factor for clinical success of UAE [88].

*e) Other Minimally Invasive Therapy*

Vaginal occlusion of the uterine arteries and uterine artery occlusion by laparoscopy (UAOL) may become one of the treatment options for symptomatic UFs [89,90]. To assess the overall effects of vaginal occlusion of the uterine arteries and UAOL, there are need in RCTs with long-term follow up.

*f) High-Frequency Magnetic Resonance-Guided Focused Ultrasound Surgery*

High-frequency magnetic resonance-guided focused ultrasound surgery (MRgFUS) is a minimally invasive technique. It introduction in 2004 by the Food and Drug Administration (FDA) for the ExAblate 2000 for the treatment of UFs. MRgFUS is a thermoablative technique using MRI. MRI is used to identify target fibroid tissues, assess proximity to critical structures and monitor tissue temperature. During the procedure, ultrasound energy waves are directed at a focal spot within a UFs (target) to be destroyed. Ultrasound energy waves heat target tissues to > 55°C, thereby resulting in protein denaturation and thermocoagulation tissue necrosis of UFs with minimal damage to surrounding normal myometrium [91]. The current platforms used for MRgFUS are the ExAblate 2000, ExAblate 2100, Sonal-leve MR-HIFU.

MRgFUS is recommended as organ-preserving treatment of patients with UFs, if the conditions are right and there are no contraindications. Potential patients with UFs are examined with MRI to localize a target tissue in 3 dimensions and determine whether they meet the selection criteria for treatment [91]. Good visualisation of the fibroid and its location, the number and size of the nodules, and the proximity of critical structures are important. Exclusion criteria are large weight, serious health complications, contraindications to MRI, abdominal scarring, uterine size greater than 24 weeks, and presence of pedunculated, highly calcified fibroids. Potential complications after MRgFUS include skin burns, nerve damage and deep venous thrombosis.

MRI-guided focused ultrasound surgery may be a promising treatment for women wishing to future conceive [92-94].

The use of UFS-QOL questionnaire before and after treatment as an informative tool for assessing the severity of UFs symptoms and quality of life may be helpful in the case of patients who have undergone alternative treatment [95,96].

## VIII. Conclusion

The clinical and social impact of UFs on population is increasing as well as the number of cases in younger women. At the same time the age of first pregnancy is increasing. Surgical treatments are still considered to be the most effective for women with symptomatic UFs, but medicine does not stop. We are convinced that the complex pathogenesis of uterine myoma suggests numerous molecular targets for open up new treatment options of these benign tumours and improving its management and that controlled research with involving specialists from different fields is needed to continue the study of UFs etiopathogenesis.

New data about pathogenesis of UFs and complete understanding the role of stem cells and their paracrine interactions, steroids, growth factors, genetic and epigenetic changes as well as their connection with each other will explore new options for prevention and help to new, effective, uterine-sparing therapeutic strategies for patients with UFs.

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# Bilateral Macular Edema Complicating Severe Pre-Eclampsia

By Fiqhi Aissam

*Abstract-* Preeclampsia, is a general syndrome that affects 5% of pregnant women, typically in the last trimester of pregnancy. It is characterized by arterial hypertension associated with proteinuria. A 25-year-old patient, with no notable pathological history, hospitalized for eclampsia and loss of visual acuity. Fundus examination shows diffuse narrowing of the arteries in both eyes, serous retinal detachment with macular retinal folds and stage 1 papilledema. OCT mapping shows retinal disorganization in both eyes inter-papillo-macular with cystoid macular edema, macular thickening and presence of a DSR . At 1 month postpartum, visual acuity was 9/10 in the right eye and 8/10 in the left eye with drying of the macular edema and serous detachment and disappearance of the papilledema.

*GJMR-E Classification: DDC Code: E LCC Code: PN1997*


*Strictly as per the compliance and regulations of:*

# Bilateral Macular Edema Complicating Severe Pre-Eclampsia

Fiqhi Aissam

*Abstract-* Preeclampsia, is a general syndrome that affects 5% of pregnant women, typically in the last trimester of pregnancy. It is characterized by arterial hypertension associated with proteinuria. A 25-year-old patient, with no notable pathological history, hospitalized for eclampsia and loss of visual acuity. Fundus examination shows diffuse narrowing of the arteries in both eyes, serous retinal detachment with macular retinal folds and stage 1 papilledema. OCT mapping shows retinal disorganization in both eyes inter-papillo-macular with cystoid macular edema, macular thickening and presence of a DSR. At 1 month postpartum, visual acuity was 9/10 in the right eye and 8/10 in the left eye with drying of the macular edema and serous detachment and disappearance of the papilledema.

## I. Introduction

Pregnancy, a real challenge for the human body, is associated with a set of physiological and pathological changes. One of the most important pathologies accompanying pregnancy is the syndrome of preeclampsia/eclampsia. Toxaemia of pregnancy, or preeclampsia, is a general syndrome that affects 5% of pregnant women, typically in the last trimester of pregnancy. It is characterized by arterial hypertension associated with proteinuria. It can be responsible for different ophthalmological manifestations. Visual symptoms affect up to 25% of patients with severe preeclampsia and 50% of patients with eclampsia, and numerous ophthalmologic manifestations have been described.

Clinical observation A 25-year-old patient, with no significant pathological history, primigravida, consulted the emergency room at 36 weeks of amenorrhea for headaches, edema of the lower limbs and bilateral visual blurring. A general clinical examination showed blood pressure at 190/130 mmHg, heart rate at 90 bpm, fetal heart rate at 130 bpm. The proteinuria on the urine dipstick was 3 crosses (3+), and the level of hepatic transaminases was high. The patient was hospitalized and an emergency caesarean was performed after fetal lung maturation. On day 1 postpartum, the blood pressure figures normalized and the edema subsided. On the other hand, the visual blurring worsened. The ophthalmological examination found visual acuity at 'counting fingers' from a distance in both eyes. The anterior segment was calm. Fundus examination reveals in both eyes, in a fairly symmetrical detachment with macular retinal folds and stage 1 papilledema (Figure. 1). OCT mapping shows in both eyes disorganization of the inter-papillo-macular retina with cystoid macular edema, macular thickening and presence of a cloudy DSR (Figure. 2) The patient was put on Acetazolamide by oral route at the rate of 250 mg 3 times a day, Dorzolamide eye drops at the rate of 1 drop x3 per day and AINS eye drops at the rate of 1 drop x3 per day. The evolution at 15 days was favorable. Visual acuity was 5/10 in the right eye and 4/10 in the left eye. At 1 month postpartum, visual acuity was 9/10 in the right eye and 8/10 in the left eye with drying of the macular edema and serous detachment and disappearance of the papilledema.

## II. Discussion

Pre-eclampsia is defined by the World Health Organization (WHO) as being the association of arterial hypertension, proteinuria greater than 300mg/24 hours or greater than 2 crosses on the urine dipstick from the 20th week of amenorrhea with or without edema of the lower limbs [1]. Severe pre-eclampsia (SPE) is defined by the appearance from the 20th week of amenorrhea of arterial hypertension whose systolic blood pressure (SBP) is greater than or equal to 160 mmHg and/or diastolic blood pressure (TAD) greater than or equal to 110 mmHg, and proteinuria greater than or equal to 3g/24 hours or greater than or equal to 3 crosses on the urine dipstick [1]. SPE can be complicated by eclampsia, which is a paroxysmal accident with dominant neurological expression, manifested by tonic-clonic convulsive seizures occurring in the context of unrecognized or untreated severe pre-eclampsia. It produces a repeated convulsive state followed by a comatose state and can occur during pregnancy after the 20th week of amenorrhea, during childbirth, or postpartum [1]. Pre-eclampsia/eclampsia is a public health problem. In fact, it is one of the three main causes of maternal mortality in the world [1, 2]. The ocular complications of pre-eclampsia are essentially due to arterial spasm and its consequences on the retinal and choroidal vascular circulation [3]. During pregnancy, pre-existing ocular pathologies can worsen, such as diabetic retinopathy and uveitis. Other ocular pathologies are specific to pregnancy and are complications of pre-eclampsia/eclampsia [4]. Visual symptoms include visual blurring, diplopia, transient amaurosis, photopsia, visual field deficit. These signs may be attributed to posterior cerebral artery

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vasospasm or cerebral edema in the occipital region. The most common ocular manifestation is the constriction of retinal arterioles found in 60-70% of cases [4,5]. Other ocular manifestations are possible such as hypertensive retinopathy, retinal detachment, vitreous hemorrhage. Serous retinal detachment is a rare cause of decreased visual acuity in pre-eclampsia/eclampsia with an incidence of approximately 1% in severe pre-eclampsia and 10% in patients with eclampsia [6] The management of pre-eclampsia/eclampsia is multidisciplinary, it is carried out by obstetrician-gynecologists, cardiologists or anesthesiologists who administer the appropriate treatment. Regular monitoring of all severe forms of pre-eclampsia is recommended by measuring visual acuity and examining the fundus to detect ocular lesions early and indicate a cesarean in time [7, 8, 9, 10-12]. The signs observed at the fundus are elements of maternal vital prognosis but especially fetal.

## III. Conclusion

Pre-eclampsia/eclampsia is a serious pathology for the mother and her future baby. It is sometimes accompanied by ocular but especially retinal lesions predicting the fetal and maternal prognosis, the early detection of which by an ophthalmologist helps to preserve the life of the mother-child couple. Because the risk for these patients of having a fetal death is one and a half times higher than in patients without lesions.

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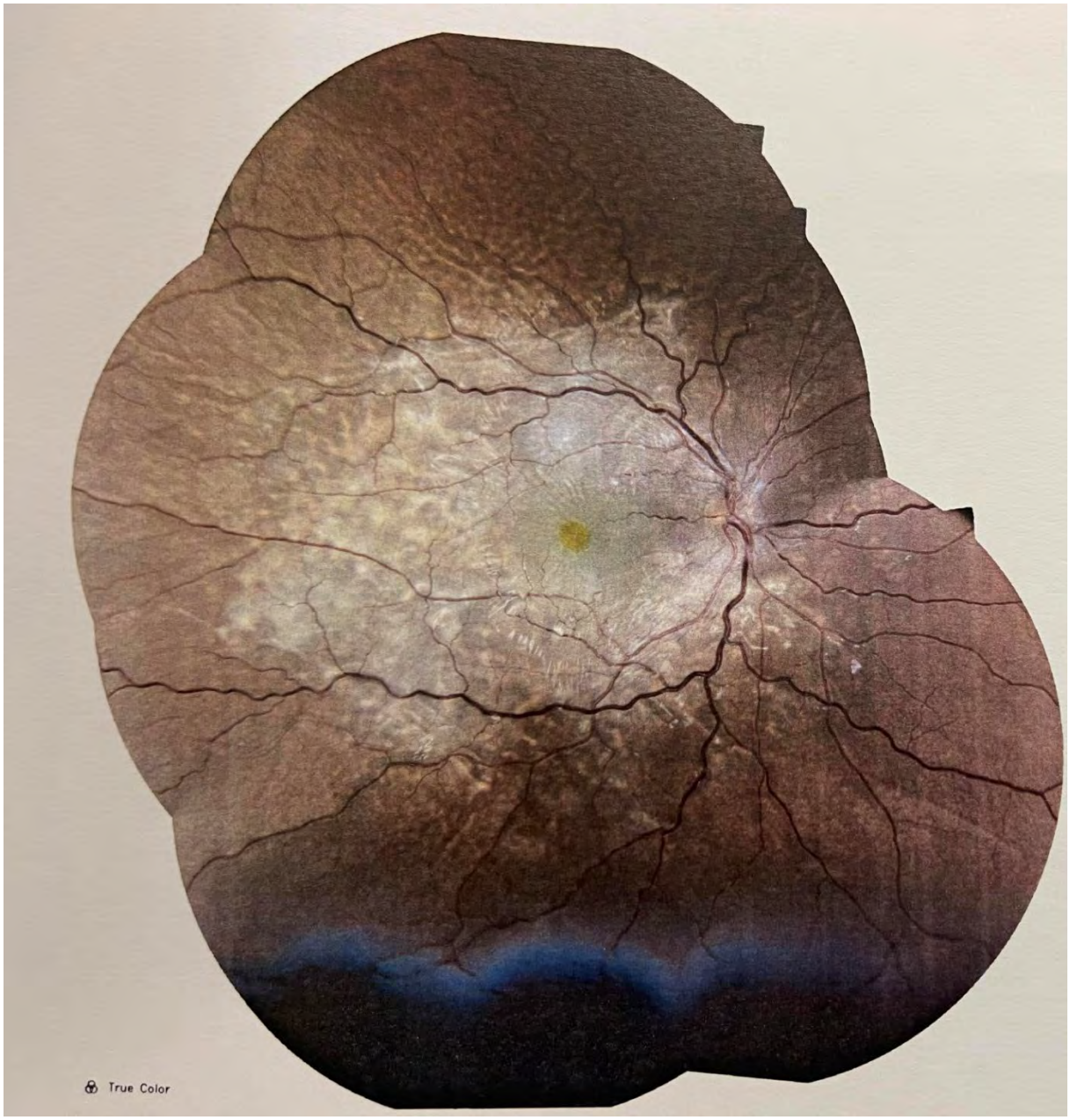

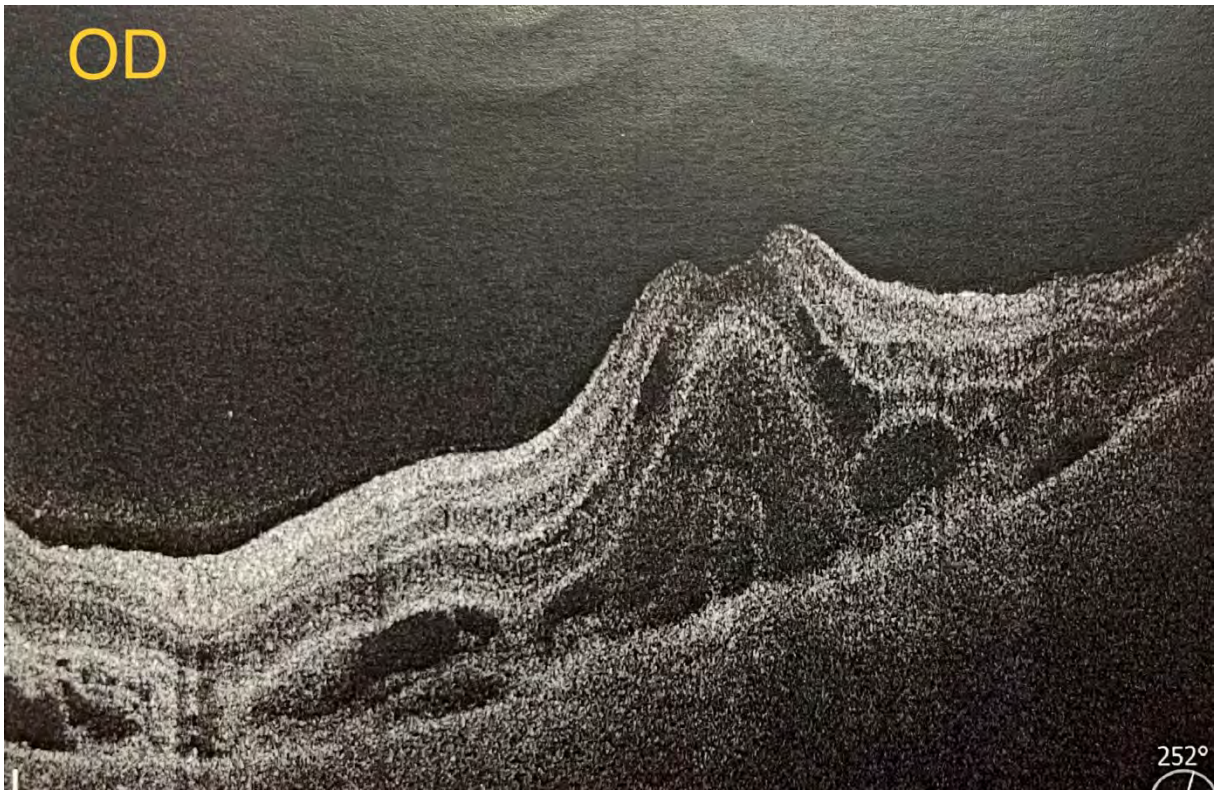


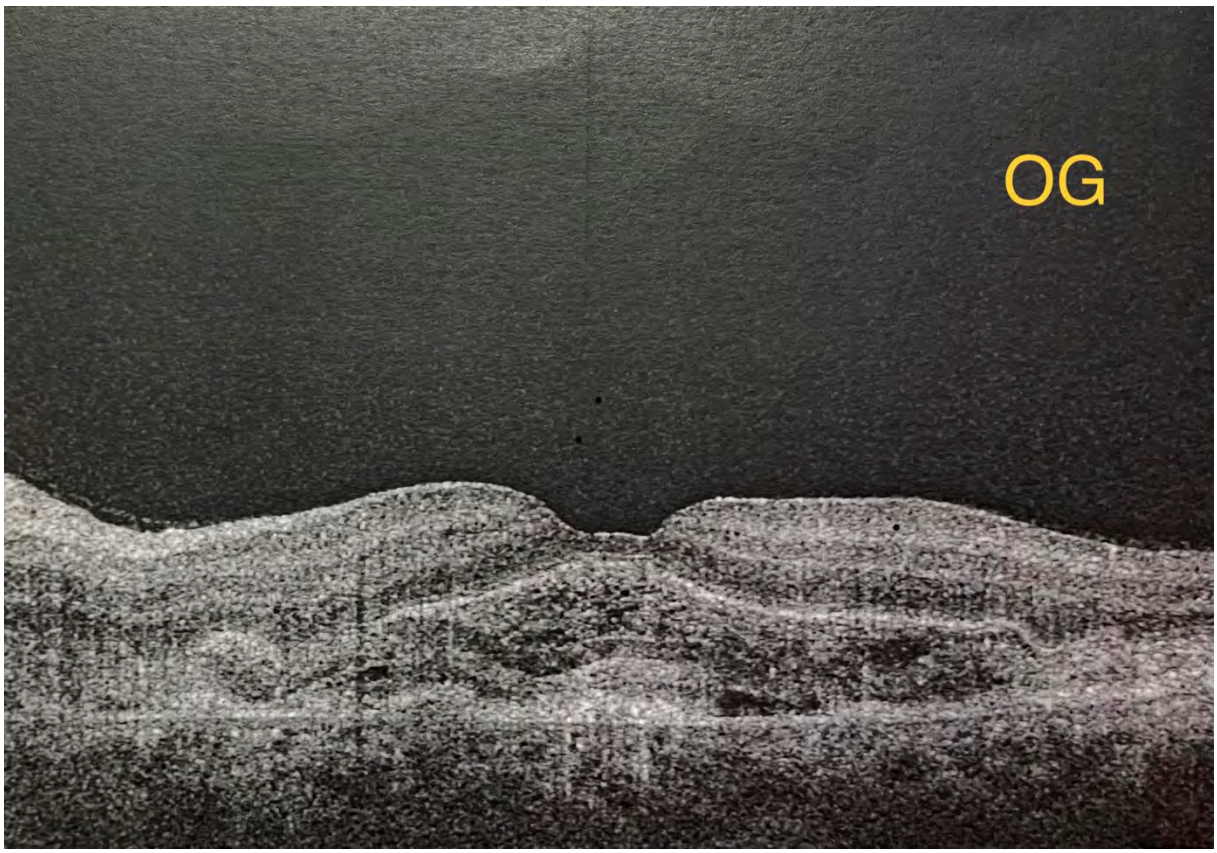

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# Role of Vitamin E and Vitamin C in Oxidative Stress of Female Reproductive System

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*Abstract-* This study is done to measure the role of vitamin C and vitamin E as an antioxidant on the oxidative stress of female reproductive system. This study explained that reactive oxygen species and oxidative stress remain in balance to prevent the human body from adverse effects of oxidative stress. This study explained that reactive oxygen species affect the multiple physiological functions of female reproductive system such as maturation of oocyte from fertilization, development of embryo, and pregnancy. This is a case study report based on the previous studies to measure and assess the findings of other scholars about the effect of vitamin E and vitamin C on the oxidative stress on female reproductive system. Thus, the results of this study concluded that Vitamin E and vitamin C act as a defense partners against oxidative stress in female reproductive system.

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*Strictly as per the compliance and regulations of:*

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## I. Introduction

The main factor in the pathogenesis of most diseases is oxidative stress (OS)(Agarwal, Gupta, Sekhon, & Shah, 2008) which arises when antioxidant and prooxidant imbalances arise (Al-Gubory, Fowler, & Garrel, 2010). Due to OS-induced cell membrane damage, DNA damage, and apoptosis, O S is implicated in faulty and delayed embryonic development. Apoptosis leads to the development, with minimal changes to implant and mature, of fractured embryos (Muriel, 2006).

Due to the metabolic rate and the growth in mitochondrial activities, Placenta may be the primary source of OS. Placental tissues have low concentrations and key antioxidant functions during the first quarter, including catalase, glutathione peroxidase, and superoxide dismutase. This condition will cause oxygen-mediated damage to the embryonic trophoblast cells (Poston & Raijmakers, 2004). As oxygen stress rose at the beginning of the maternal bloodstream, a placental OS explosion had been observed in the second quarter. Analysis shows that this oxidative damage can have a detrimental effect on the placental remodeling and functions that may change the course of gestation (Metcalfe & Alonso, 2010).

Excess prooxidants cause OS by either the production or inhibition of reactive oxygen species (ROS). ROS's reactivity is extremely unstable. They gain electrons from acid, lipid, protein, carbohydrate, or some other surrounding molecule that makes a chain of reactions stable. These reactions in the chain contribute to cellular disruption and sickness. ROS can damage cell functions in the female reproductive system and can ultimately stop homeostasis intracellular and contribute to damage to cells (Mohd Mutalip, Ab-Rahim, & Rajikin, 2018).

Excess ROS also influences early embryonic development by altering the primary transcription factors modifying gene expressions (Dennery, 2004). High levels of ROS can also adversely impact oocyte fertilization and hinder embryonic implantation in the female reproductive tract. High ROS development and reduced defense antioxidant potential may contribute to increased sensitivity to OS for the developing fetus (Sharma & Agarwal, 2004).

The overproduction of ROS is limited by antioxidants. They are in both enzyme and non-enzyme forms. They are there. The natural antioxidants or endogenous antioxidants are known as natural antioxidants or endogenous antioxidants are known as enzymatic antioxidants (SOD), catalase, but oxidase GSH, and reductase glutathione (GSH). Available from foodstuffs and vegetables are the non-enzymatic antioxidants, also known as the exogenous antioxidants. Taurine, hypotaurine, β-carotene, selenium, copper, vitamin C, and vitamin E are among others (Agarwal, Gupta, & Sharma, 2005).

As an antioxidant of female reproductive health, vitamin C and vitamin E are a good defense in retarding free radical cellular injury, shown to be helpful for breastfeeding and neonatal health, and have played an important role in disorders of fertility or pregnancy. Vitamin C serves as a reduction agent for cell safety against adverse OS effects (Shaik-Dasthagirisaheb et al., 2013). Vitamin E acts to defend cell membranes from ROS and as a chain-breaking antioxidant, for example in protection against auto-oxidation by polyunsaturated fatty acid (PUFAs) (Traber & Atkinson, 2007).

The main element for the pathogenesis of most diseases is oxidative stress and when imbalances arise in the presence of antioxidants and pro-oxidants. Because of cell-membrane injury, DNA damage, and apoptosis triggered by OS, the incomplete and delayed embryonic growth includes OS. Apoptosis contributes to the development of broken embryos that are less likely to implant and increase. ROS and antioxidants remain in equilibrium in a balanced body and the reactive oxygen molecules. Oxidative stress (OS) happens when the

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equilibrium is broken to an overabundance of ROS. OS affects the entirety of a woman's reproductive life and even afterward OS stems from an excess of the capacity of the body to scalp prooxidants (antioxidants) and (free radical species) (Roth, 2017).

ROS is a double-edged weapon - signal molecules that act as the most important in physiological processes but also have a role in female reproductive processes. ROS affects many physiological pathways, ranging from oocyte to fertilization, fetal growth, and conception. It was proposed that OS modulates the decrease in fertility associated with age. It plays a role in and initiates premature jobs during pregnancy and natural parturition. In the superficial epithelium, most ovary cancers occur, and prolonged ovulation was assumed to have caused them (Grandi et al., 2015).

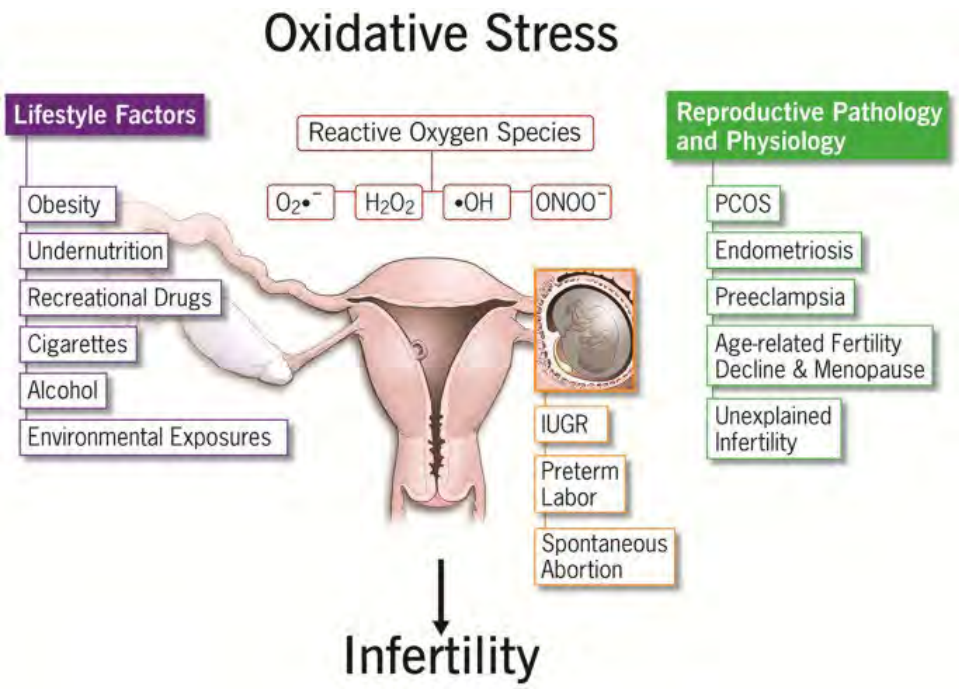


*Figure 1.0:* Oxidative Stress

OS findings of women's breeding are increasing in pre-eclampsia pathophysiology, hydatiform mole, free birth failures that lead to radical induction, and other conditions such as abortion. Many studies have shown that OS has a role to play in infertility and pathophysiology promoted fertility. Endometriosis, miscarriage, and unexplained infertility of tubes and peritoneal factor have shown their role. This article discusses the OS's role in ovaries, follicles, and endometrial cycling in daily circulation.

It also addresses female infertility associated with SA and how it impacts the effects of assisted reproductive techniques. The paper discusses the role of oxidational stress in conditions like abortion, pre-eclampsia, hydatidiform mole, fetal embryopathy, preterm labor, pre-eclampsia, gestational diabetes in a detailed way. The research also discusses the increasing role of nitrogen oxide species in women's reproduction. The functions played by nitric oxide species in endometrial or ovarian control, endometriosis etiopathology, or maintaining uterine relaxation, labor, and cervical ripening throughout gestation are addressed (Patel et al., 2015).

Radical species free and strongly reactive are unstable. It is stable when the electrons are obtained from nuclear acids, lipid, protein, and carbohydrates, or other molecules which, via chains, lead to cellular oxidative stress-induced. There are 2 main types of free radical molecules: reactive oxygen (ROS) and nitrogen species Reactive (NOS).

Vitamin E was first found to be a sexual substance in 1922. Vitamin E has been researched thoroughly and is now commonly recognized as a potent fat-soluble antioxidant after this discovery. The role of vitamin E as an antioxidant is increasingly interested since it has been discovered as an anti-cancer agent and lowers body cholesterol levels. Many studies have shown that the influence of vitamin E on cancer and anti-inflammatory activities include, anti-angiogenic anti-survival, anti-proliferative, and anti-apoptotic effects. Vitamin E's health benefits usually are recorded in different ways. Although it has initially been shown to be a reproduction-related vitamin, research concerning its effects is still missing in this field. This paper is therefore intended to explore the known functions of vitamin E in women's reproductive health as an antioxidant (Jung et al., 2012).

## II. Oxidative Stress

Julein Finaud et al. (2012) conducted a study to explain that what is oxidative stress. Free radicals are known as highly reactive compounds that are naturally produced in the human body. This study explained that oxidative stress has both positive and negative effects on the body. The positive effects of free radicals activate the immune system of an individual whereas the negative effect of free radicals in the oxidation of lipids, proteins, and DNA within the human body. There is a need for complex protection from the protection of harmful effects of these oxidation reactions this system is known as the antioxidant system. This study explained that the antioxidant system is comprised of antioxidant enzymes and non-enzymatic enzymes. Some examples of antioxidant enzymes of this system are catalase, superoxide dismutase, glutathione, and catalase, whereas the examples of non-enzymatic antioxidants are vitamin E, glutathione, vitamin A, uric acid, and vitamin C. The presence of an imbalance between the production of these free radicals and the antioxidant defense system leads to a state known as oxidative stress. The state of oxidative stress involved in the again processes and also leads to some diseases such as cancer and Parkinson's disease. When an individual has done physical exercise it increases the oxidative stress of an individual and results in the disruption of homeostasis. The training of individuals also imparts positive as well as negative effects on oxidative stress. The presence of this stress on the human body depends on the training load, basal level of training, as well as training specificity of an individual. This study also explained that oxidative stress results in Muscular fatigue due to the presence of oxidative stress due to excessive training (Julien Finaud, 2012).

Helmut Sies et al. (2017) conducted a study to explain the facts about oxidative stress. This study explained that oxidative stress is two-sided such as it is beneficial for human beings but its excess may also cause multiple diseases within the human body. This study explained that the presence of oxidant challenge within the human body causes severe damage to the biomolecules, an essential component for the governing of life processes by redox signaling, maintenance of a physiological level of oxidant challenge, and also termed as the oxidative eustress. This study has determined that recent studies focused on the intricate ways by which all redox signaling of oxidative integrate its all converse properties. The maintenance of redox balance is done by the prevention, concomitantly, interception, and repair of the regulatory potential of molecular thiol-driven master switches. This study explained that these thiol-driven switches such as Nrf2/Keap1 or NF-κB/IκB are most commonly used for the oxidative stress response. This study explained that the presence of non-radical species such as hydrogen peroxide as well as singlet molecular oxygen performs its functions as a major second messenger function to prevent the disease. This study explained that chemokine-controlled NDPH oxidases as well as metabolically controlled mitochondrial sources, and thioredoxin-related pathways with the presence of a powerful enzymatic backup system imparts an important role in the fine-tuning of the physiological redox signaling. This study imparts an important role in redox medicine based on its nutritional science, molecular knowledge of the product, and environmental medicine (Helmut Sies, 2017).


*Figure 2.1*: Cells in Oxidative Stress

## III. Vitamin E and Vitamin C as Defence Partners

Alvin et al. (1993) conducted a study to explain that vitamin E and vitamin C are partners in the defense system. This study explained that free radicals and oxidative stress within the human body can also reduce by the presence of vitamin E and vitamin C. Enzymes are majorly involved in the removal of free radicals from the human body by act as scavengers of free radicals but the presence of some vitamins also act as the strong line of defense in reducing the free radicals by induced cellular damage. This study explained that various distinct pathways are used for the repairing of oxidized vitamin E in human cells have been identified in this study. This study explained that when arachidonic acid is imparted in the human body, after 0.5 minutes of this addition or installation the half of the platelet vitamin E added with the arachidonate was metabolized by enzymes named platelet cyclooxygenase and lipoxygenase pathways. This study explained that after the addition of nordihydroguaiaretic acid, which is a strong reductant and a lipoxygenase inhibitor was regenerated to form vitamin E. This study explained that there is a need to test the various physiological and water-soluble reductants that helped in regenerating the vitamin E, lipoxygenase inhibitory, and eicosatetraenoic acid that is not antioxidant was used. The use of both ascorbate, as well as glutathione present in the human body, imparts a significant and remarkable role in the regeneration of vitamin E. the kinetic analysis of regeneration of vitamin E and previous studies about vitamin E explained that its regeneration is done by a system-denaturing system that revealed that ascorbate imparts an important role in its regeneration. The regeneration of vitamin E is done both either by use of enzymes or without the use of enzymes in enzymatically regeneration glutathione is included but in non-enzymatically ascorbate is used. This study determined that there is a remarkable and significant relationship present between the water-soluble and lipid-soluble molecules at the membrane-cytosol interface as well as vitamin C also involved in the repairing of oxidized vitamin E. Thus this study explained that vitamin E and vitamin C imparts an important role in the defense mechanism against the oxidative stress present in the human body (Chan, 1993).

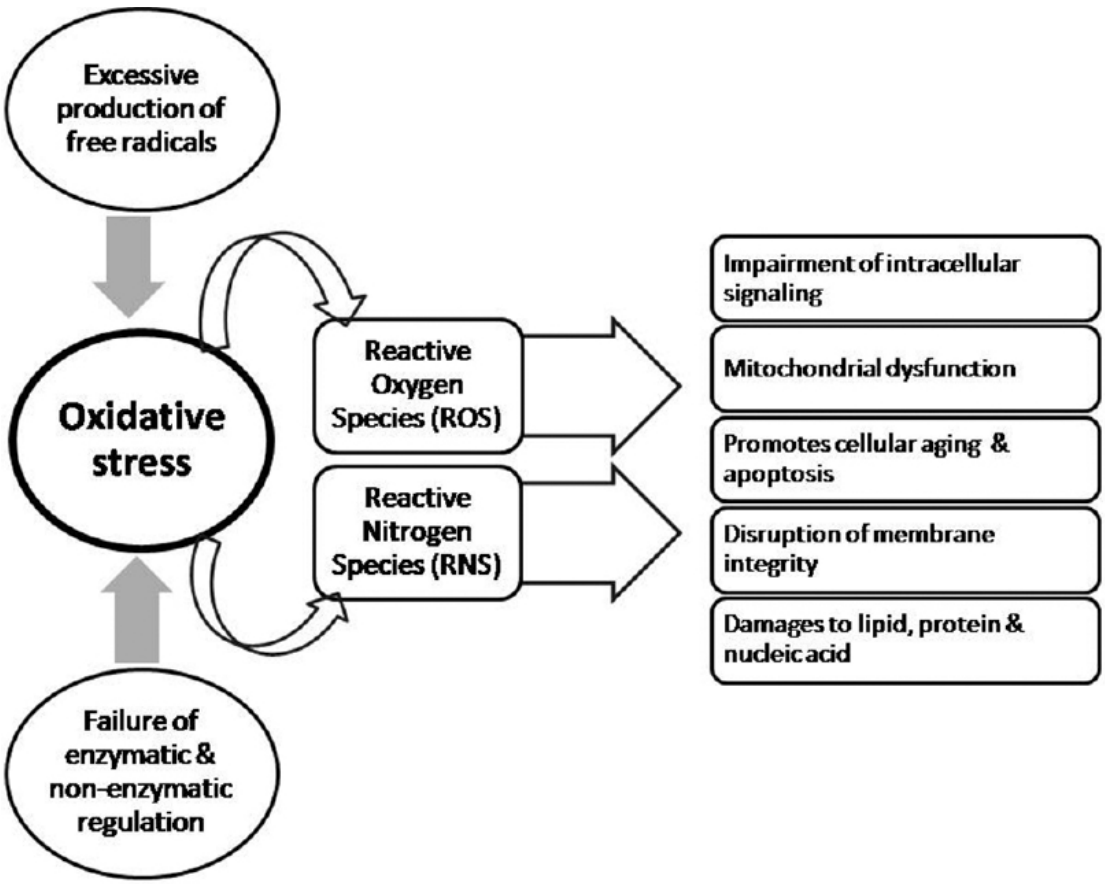


*Figure 2.2:* Excessive Production of Free Radicals

Senousey et al. (2018) conducted a study to explain the role of dietary vitamin C, vitamin E, and alpha-lipoic acid supplementation on the antioxidant defence system and also immune-related gene

expressions exposed to oxidative stress by the dexamethasone. This study explained that vitamin C, vitamin E, and ALA are known as some of the potential nutritional antioxidants that impart an important role in enhancing the immunity of an organization. The powerful nutritional antioxidants Vitamin C, Vitamin E, and Alpha-lipoic acid (ALA) is helpful in the improvement of the immune. The effects of the vitamin C, vitamin E or ALA supplementation on the antioxidant system and the immune-related expression of the genes under oxidative stress generated by dexamethasone (DEX) in broilers were compared in this study. In all, 240 one day females Recessive White Rock have been allocated to basal diets, either with a vitamin C supplement (200 mg/kg diet), with vitamin E supplements (100 mg/kg), or ALA (500 mg/kg) randomly with a 28 d commencing from a hatch.

This study explained that at the 21d age, birds fed ALA-supplementation that imparts an important role in their total antioxidant capacity, increases the superoxide dismutase, enhances the activities of glutathione peroxidase, and also lower the malondialdehyde activities. This study explained that the use of ALA supplementation also reduced the levels of mRNA gene expressions of interferon gammas as well as lipopolysaccharide-induced tumor necrosis factor-alpha factor. In the 3 therapeutic groups, the broilers were injected with DEX into the thigh muscle for 3 alternative days at the age of 23 d. The control group was also separated in 2 equal groups, one injected with saline and the other with DEX. At 28 d of age, the plasma and liver DEX-ALA ($P < 05$), and the biggest decreases in the MDA, were at the highest levels of activity for T-AOC, T-SOD, and GSH-PX ($P < 0,05$). Dietary ALA significantly lowered the interleukin 1β, IL-6, IFN-β and LITAF expression levels than other groups during oxidative stress by DEX. During the oxidative stress period the ALA was considerably less. Finally, this study indicates that ALA is higher in broilers (H.K.El-Senousey, 2018).

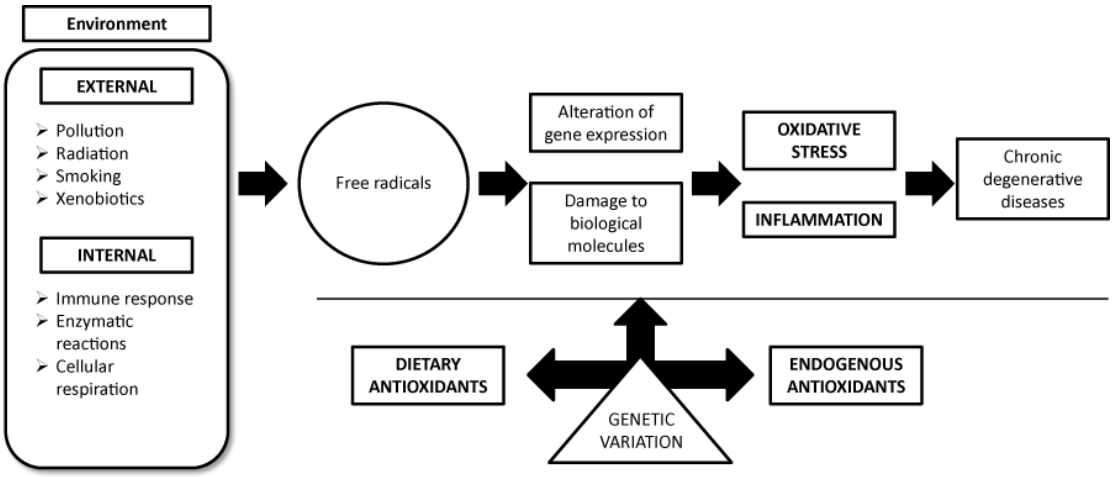


*Figure 2.3:* Genetic Variation

## IV. Role of Vitamin E and Vitamin C in Oxidative Stress of Female Reproductive

a) *Character of Oxidative Stress on the Reproduction of Female*

A 2005 research by Ashok Agarwal et al. on the role of oxidative stress for women. This study determines that ROS and antioxidants present in our body on a balance and when this balance is disturbed the physiological functions of the human body are also disturbed. OS highly influenced the lifespan of a female reproductive system and after menopause, there is imbalance occurred between the ROS and antioxidants present in the body. ROS act as the signaling molecule present in the body and also have some pathological properties, especially in the female reproductive system. This study determined that ROS affects various physiological processes such as fertilization, oocyte maturation pregnancy, and embryo development.

This study also explores the fact that OS is involved in age-related weakening infertility. OS imparts a significant character in the pregnancy, normal parturition, and also in the initiation of the preterm labor. It was determined that repetitive ovulation and surface epithelium were the main causative factors of ovarian cancer in the female reproductive tract. Antioxidant damage to the ovarian (Agarwal et al., 2005).

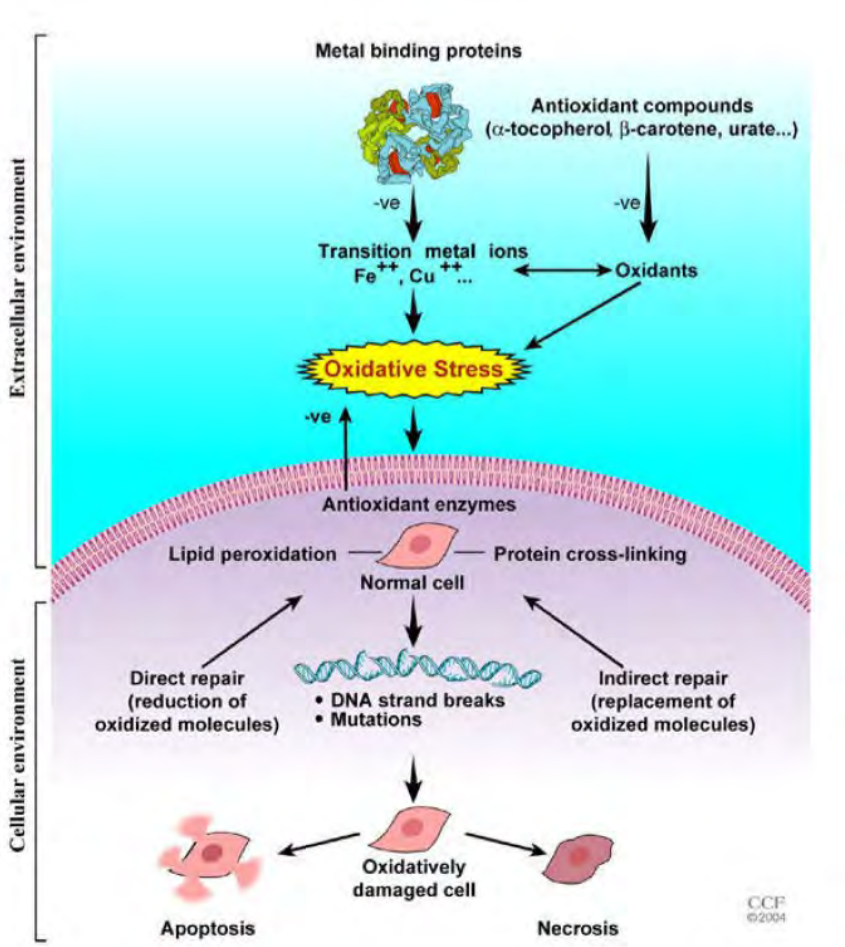


*Figure 2.4:* Metal Binding Proteins

Oxidative basis and damage to the DNA incurred by epithelial ovulation can also be prevented. OS literature is increasing with the involvement of pre-eclampsiological pathophsiology, mole-hydatide and free radical contamination, and in other cases, such as abortions. More and more detail is available. Many studies have shown that OS plays a part in infertility and fertility pathoysiology. The function of endometriosis, peritoneal and tubal infertility and unexplained infertility are seen.

In the aetiology of female reproductive disturbances, the dynamic interplay between cytokines and oxidative stress is discussed. The cell's oxidants modulate angiogenesis, which is crucial to follicular development, endometrial differentiation of corpus luteo formation and embryonic growth. Oxidative stress control techniques and reproductive enhancement are both normal and assisted. Early measures for pre-eclampsia prevention are mentioned. Trials exploring vitamin E and vitamin C intake in combination intervention methods are illustrated in pre-eclampsia prevention. Antioxidants are high and antioxidant supplements in the sexual breeding have been studied in several studies. However, in order to show the effectiveness of antioxidant supplementation in female reproductive disorders, randomised controlled experiments with adequate strength are needed until doctors prescribing antioxidants. In longitudinal research, serial measurements of oxidative stress biomarkers may help delineate the aetiology of certain diosorders such as preeclampsia for reproduction by females (Staff, 2019).

*b) Impact of Oxidative Stress on Female Fertility*

Elizabeth et al. conducted a study to determine the impact of oxidative stress on female fertility. This study determined that oxidative stress is related with decreased female fertility in multiple animals but there is no any direct relation with the women. Oxidative stress-related exposures and proofs of timing and sustaining a viable birth include risks of pregnancy (e.g. preeclampsia), extremes of body weight, alcohol and nicotine as well as caffeine use. The consumption of antioxidant nutrients, like multivitamins, has repercussions on the production of reactive species of oxygen and can support women's fertility. Infertility is a huge public health issue and frustrating, intrusive, and expensive diagnosis and care. An understudied and

convincing area of study is the role of the oxidative stress in female fertility. Identifying modifiable stress relief mechanisms may be an effective and invasive treatment for increased fertility in the gynaecological setting (Ruder, Hartman, & Goldman, 2009).

*c) Character of Oxidative Stress on the Reproduction of Female*

A research by Jiayin et al. to determine the role of oxidative stress in reproductive women was carried out. This research was carried out to examine the significance of oxidative stress in the reproductive system for the woman. There are multiple studies have been done on this topic as this topic become very common regarding the research. The oxidative stress (OS) analysis has become more and more common in recent years. The role of the OS in women's fertility is especially significant and closely oriented.

OS occur when overproduction is achieved by reactive oxygen species (ROS).

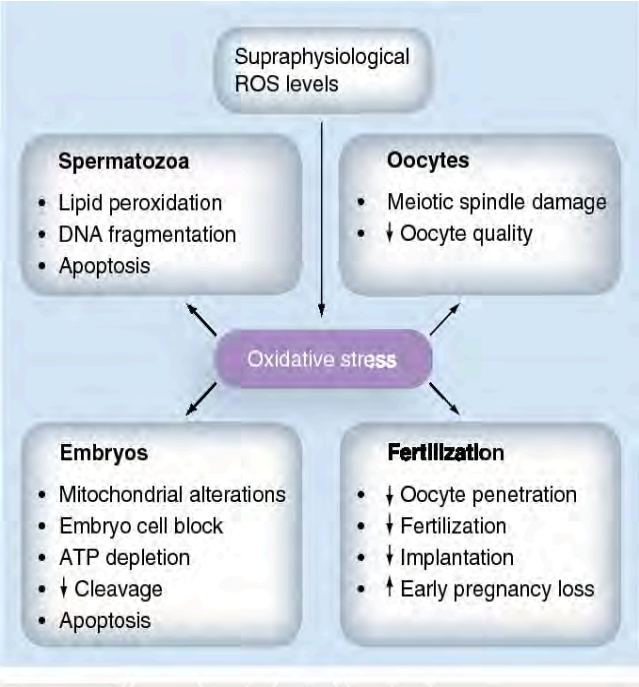


*Figure 2.5:* Supraphysiological ROS Levels

In certain intracellular cascades, ROS is a two-edged sword; as secondary Messengers, it not only plays an important part but it also has important effects on pathological processes involving women's genital tract. In this study it was explored that reactive oxidative stress as well as anti-oxidants imparts an important role in the regulation of the reproduction of both animals and humans. Both animals and people are governed by ROS and antioxidants for reproductive processes. Disorders between prooxidants and antioxidants may lead to many reproductive illnesses in women. This analysis focuse on the function of OS and a variety of reproduction processes for women, describing the role of OS in women's reproduction and OS-generated reproductive diseases, including PCOS, endometriosis, preeklampsia, etc. A variety of signals affecting female fertility, including the OS-affected pathways of the Keap1-Nrf2, NF-ŢB, FOXO, and MAPK, offer new insights into processes of reproductive diseases (Lu, Wang, Cao, Chen, & Dong, 2018).

*d) Vitamin E and Vitamin C as Defence Partners*

The protective essence and relationship of vitamin C and vitamin E has been determined by Alvin Chan et al. Besides the enzyme free radical removal process, essential foods, such as vitamins E and C, that can scavenge free radicals, form a powerful protection to delay free radical damage to the cell. Different mechanisms have recently been established to fix oxidised vitamin E in human cells. About half the vitamin E platelet and the addition of arachidonate is metabolised by platelets cyclooxygenase and lipoxygenase pathways within 0,5 min of the addition of arachidonic acid to the human platelet homogenate. More than 60% of the oxidised vitamin E was regenerated after adding Nordihydroguaiaretic acid, a lipoxygenase inhibitor and a good reducing agent.

There were multiple physiological and water-soluble reducing agents were testes to explore that they may help in regenerating of the vitamin E as well as eicosatetraenoic acid that is a lipoxygenase inhibitor was used for this test. In testing of other physiologically soluble water-reducing agents, eicosatetraenoic acid, an inhibitor of lipoxygenase, which is not an antioxidant, can help regenerate vitamin E. Ascorbate and glutathione have been essential for the regeneration of vitamin E in this phase.

Kinetic analyses and analyses of the regeneration of vitamin E within a protein denaturation system have shown that ascorbate regenerates vitamin E by a nonmammal process, while glutathione enzymatically regenerates vitamin E. These studies indicate that essential interactions occur at the membrane cytosol interface between the water- and lipid-soluble molecules and that vitamin C can function in vivo to repair the membranous oxidising vitamin E (Wong et al., 2019).

*e) Review about Role of Oxidative Stress in Female Reproduction*

The Jiayin et al. researched the effect and role of oxidative stress within reproduction of women from various scientists. They performed a review. The oxidative stress (OS) analysis has become more and more common in recent years. The role of the OS in women's fertility is especially significant and closely oriented. OS arise when reactive oxygen species are overly production (ROS). In certain intracellular cascades, ROS is a two-edged sword; as secondary Messengers, it not only plays an important part but it also has major impacts on pathophysiological

conditions involving women's genital tract. Both animals and people are governed by ROS and antioxidants for reproductive processes. There were some imbalances occurred between the pre-oxidants and antioxidants and this imbalance imparts a great role in the production of multiple diseases of female reproductive.

ROS is a two-edged weapon in some intracellular cascades; as second Messenger it plays a critical role, and also has a significant effect on pathophysiological disorders affecting the reproductive tract of women. A large number of signalling pathways in female reproduction are identified, including the OS-affected Keap 1-Nrf2, NF-ŚB, FOXO and MAPK pathways, offering a new insight into reproductive disease mechanisms (Lu et al., 2018).

*f) Part of Oxidative Stress on Assistant Pregnancy*

The research by Gupta Sajal et al. has explored the role of oxidative stress on an adjunct. There were multiple disease s happened due to the presence of oxidative stress and also seen that this oxidative stress resulted in the failures of techniques by which pregnancy and fertilization has achieved. Oxidative pressure leads to the high rate of failing to accomplish fertilisation and conception in assisted reproduction techniques. Several experiments have been undertaken to explain the cause of oxidative stress on ART and to resolve the detrimental impact it has upon IVF and ICSI outcomes. This research deals with the use of metabolomics as a modern and non-invasive process to reliably and efficiently measure oxidative stress. A literature review on the results of various treatments to boost the levels of fertilization and conception is at the core of this research. This research aims to updates the current literature on findings from various therapies including the use of antioxidant supplementations for IVF cultures and patients to improve the fertilization and reproduction rates of key is to avoid patients receiving ART (Gupta, Sekhon, Kim, & Agarwal, 2010).

This study determined that oxidative stress is highly connected with the negative ART outcomes. Oxidative tension is associated to poor ART performance. The literature has been well developed for both exogenous and endogenous sources of reactive oxygen species during IVF/ICSI. In contrast to IVF, gamet susceptibility to endogenous oxidative stress sources in gametes is considered to reduce. There are multiple strategies present for the management of exogenous causes of oxidative stress include minimising visible/near sensitivity to UV light, the incorporation of metal chelators to cultivated media, preserving environmentally low oxygen voltage and the use of antioxidant therapy. A vitamin C, vitamin E and melatonin antioxidants supplement of culture media have been studied and conflicting results have been made (Khazaei & Aghaz, 2017).

Although oral antioxidant supplementation has been recognized for male patients and is currently performed, the efficacy of vitamin C, vitamin E, and melatonin supplementation for females undergoing ART is not being decided. A further study of the effectiveness and safety of antioxidant supplementation in culture media and patients is important in randomized controlled trials, along with a determination of the dose necessary for optimizing IVF/ICSI fertilization rates and pregnancy outcomes.

*g) Vitamin E for the Health of Female Reproductive System*

A research was performed to determine vitamin E as the health of women in the reproduction system by Syairah Mohd Mutalip et al. This study has been done to determine that how vitamin E imparts a significant part on the health of a female reproductive system. This study determined that the importance of vitamin E as a reproductive substance has been discovered in 1922. Vitamin E has been researched extensively and is commonly recognised as a strong lipid-soluble Antioxidant after the finding. Since it was seen to be less cholesterol in body and an anticancer agent, vitamin E's performance as an antioxidant has increased. Vitamin E has been noted in several trials for anti-proliferative, anti-survival, pro-apoptotic, anti-angiogenesis and anti-inflammatory roles in cancer (Wong et al., 2020).

Vitamin E gave the multiple benefits to the human health and is very important in the maintenance of healthy life of a female. It also imparts an important and positive role on the health of female reproductive system. Vitamin E's health benefits in general are recorded in different ways. While it is initially discovered as a reproductive vitamin, research on its effects in this region have been incomplete to date. In order to assess the known functions of vitamin E as an antioxidant for the reproductive health of women, this paper was therefore drafted.

*h) Effects of Vitamin E and Vitamin C Supplementation on Female Reproductive System*

Jennifer Mier-Cabrera et al. also conferred a review on peripheral oxidative stress markers and fertility rates in endometriosis women to examine the effects of vitamin E and Vitamin C supplementation. The basic purpose and goal of this research is to establish if the addition of Vitamin E and Vitamin C imparts a significant part on the health of female reproductive system. Vitamin C and Vitamin E reduces oxidative stressors in women with endometriosis and also increases pregnancy rates. The vitamin C and E bar (specifically 343 mg and 84 mg, respectively) and 6 months placebo were obtained by 344 women with endometriosis. Plasma and peritoneal fluid (MDA) and lipid hydroperoxides have been tested for both women and in both grades (LOOHs) (Vitale et al., 2018).

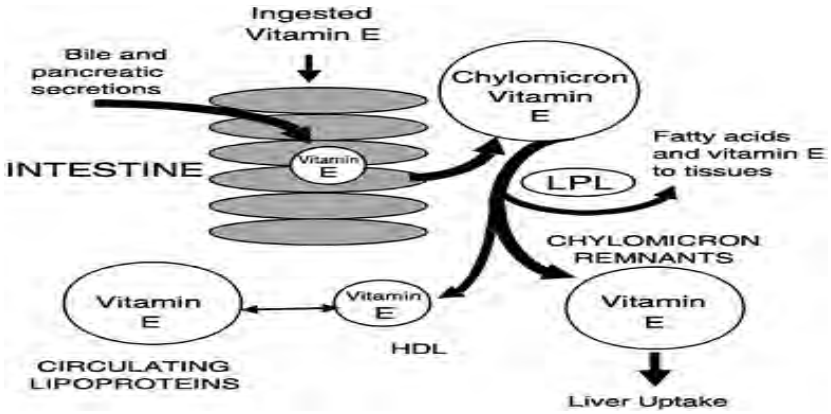


*Figure 2.6:* Bile and Pancreatic Secretions

The analysis of data is important to determine the actual result and conclude the outcomes of the study. The analysis of a data has been done by multiple ways such as t test, chi-square test, correlation, and other multiple test. Data for quantitative variables and a Summer Test of Man—Whitney, or a Kruskall-Wallis test for nonparametric data were tested by the t or 1-way study of variances. For comparing pregnancy rates, the exact Fisher test was used. After 4 months the MDA and LOOH were smaller than the control group. The difference was statistically meaningful in the fourth months for MDA and in the sixth month for LOOHs. The pregnancy rates were 19 percent and 12 percent in the supplementation and placebo categories, both of which showed no substantial difference. The conclusion is that a decrease in the oxidative stress markers in women with endometerosis is consistent with the supplementation of vitamins C and E. However, before or after the procedure the pregnancy rate did not change (Mier-Cabrera, Jiménez-Zamudio, García-Latorre, Cruz-Orozco, & Hernández-Guerrero, 2011).

*i) Follicular Fluid and Serum Markers of Oxidative Stress in Women Infertility*

Laura Prieto et alstudy.'s has measured follicular fluid and serum oxidative stress markers in women with endometriosis-related infertility. The goal is to investigate the levels of four oxidative stress markers in follicular fluid and plasms in endometriosis and control-related infertility patients. It is an experimental study design and conducted within a university affiliated hospitals and infertility center. Ninety one women has been participated in this study from which 23 women were infertile with endometriosis and 68 women control due to the presence of tubal factor, healthy egg donors, and male factors.

Endometriosis women demonstrated lower FF levels of vitamin C (12.7 ± 5.9 vs 9.7 ± 6.9 μg/mL) and lower plasma levels of the superoxide dismutase (0.9 ± 1.4 vs. 0.5 ± 0.7 U/mL) in comparison to controls. In women suffering from endometriosis (8.1 ± 3.8 vs. 5.2 ± 3.2 μg/mL), Vitamin E plasma was substantially higher. Women with endometriosis have no significant tendency towards a lower plasma malondialdehyde concentration. These results indicate that infertile women with endometriosis have less antioxidant ability. While reactive oxygen species need a certain amount of physiological conditions, a changed equilibrium between pro-oxidant and antioxidant activities could influence folliculogenesis and adequate embryonic growth (Prieto et al., 2012).

*j) Impact of Multivitamin and Supplementation on Fertilization*

Okan et al. have completed a multivitamin and supplementation analysis to establish oxidative stress and antioxidant vitamin levels in women experiencing in vitro fécondation in serum and follicular fluid. The basic aim and objective of this study is to determine the impact of multi vitammin and supplementation modulates on the undergoing fertilization happened in vitro. In serum and folicular fluids, 56 women under IVF and 13 years of age have been tested for the effects of multivitamins and mineral additives on lipid peroxidation, diminished glutathione, glutathione peroxidase, vitamin A, vitamin C and vitamin E. We also hypothesised that the antioxidant protection mechanism may be improved by decreasing oxidative stress in the serum and follicular fluid of women suffering from IVF (Özkaya & Nazıroğlu, 2010).

*k) The Position of Free Radicals in Women's Breeding Conditions*

A research to determine the role of free radicals in female reproductive disorder and supporter reproduction was conducted by Ashok Agarwal et al. The basic aim and objective of this study is to determine and explore the role of free radicals in the female reproductive diseases. This study explored that infertility has become a very common problem that has been experienced by multiple couples. Infertility is a recurrent concern that many partners face. There are multiple treatment strategies and therapies for female infertility are available.

In certain cases, however, the procedure is observational, as the aetiology of infertility is not well known. Reactive oxygen species has been shown to play a major role in the day-to-day life of women and in infertility pathogenesis. Reactive oxygen species may also play a part in other diseases of women, such as endometriosis, and multiple sexual illnesses have arisen because of reactive species of oxygen.

If a disparity exists in the reproductive tract between Ros production or antioxidants scotching ability, oxidative stress occurs. Both normal and aided fertility are impaired. Since aided breeding approaches are widely utilized for the treatment of infertility, in vitro complications involving both fertilization and embryonic growth are important to recognize. Treatments that alleviate oxidative stress may benefit infected women suffering from diseases caused by this condition (Pashkow, 2011).

The techniques include the detection of the source of excess ROS generation, the treatment of the root cause and the supplementation of antioxidants in vitro and in vivo. Research is underway to describe and establish successful methods to combat oxidative stress in the aetiology of female reproductive diseases caused by ROS (Steller, Alberts, & Ronca, 2018).

*l) Human Reproductive Device Antioxidant Strategy*

Rosaria Meli et al. carried out an oxidative stress and BPA toxicity interaction analysis. In this study an oxidative approach has been used for the dysfunction of male and female reproductive system. Bisphenol (BPA) has been used and detected in many consumer goods and food stuffs as a non-persistent, anthropogenic and chemically pervasive compound and hence prolongs human display. Oversight of the fundamental molecular mechanism of BPA toxicity has been shown over the last ten years in several studies and the link between BPA-induced oxidatives, male and female genital defects and human diseases has been found.

The BPA exhibits tissue effects in target cells due to its hormone-like properties, inducing poisoning, Oxidative stress and inflammation-related cell responses in particular hormone receptors. It is a metabolic and endocrine disrupter. By raising oxidatively engaged mediators or decreasing the amount of antioxidant, BPA diminishes the redox homeostasis, induces mitochondrial dysfunction, modifies pathways for cell signals and contributes to apoptotic cell death.

This research analyzes BPA literatures, in which the oxidative stress induction of the toxic impact pathways of BPA that have pleotropic reproductive effects can be called the 'fil rouge' (fil rouge). The positive properties observed in male and female reproductive functions for BPA counteract the protective properties of five forms of antioxidants, namely vitamins or co-factors (herbs or plant chemical compounds), methyl donor, melatonin, and selenium products, are localized here (used individually or in a combination) (Zaid, Othman, & Kassim, 2018).

*m) Role of Vitamin C on Female Reproductive System*

Mustafa Saygin et al. conducted a study to determine the impact of electromagnetic radiation on the female reproductive system and also determine the role of vitamin C on the female reproductive system. The present research has researched the effects of the 2,45 GHz continuous electromagnetic (EMR), which could cause the ovarian, fallopian and uterine tissue changes in physiopathology or morphology. We proposed to reduce these extreme effects with the addition of vitamin C (Vitamin C). Eighteen sprague Dawley rats have been split randomly into three groups of five animals in each:, EMR, EMR, 1 h/day for 30 days and Sham and Vitamin C.

In the EMR only category of ovarian tissues, the average status of oxidants and the oxidative stress index (OSI) improved ($p = 0.011$ and $p = 0.002$, respectively). In the Vitamin C-treated community in fallopian tube, and ovarian, and uterine tissues ($p < 0.05$) the TOS and OSI levels decreased substantially in all tissues. The level of anti-muller hormones in the EMR group ($p<0.05$) was slightly increased and in Vitamin C-treated groups was decreased. In the EMR group, estrogen (E2) levels had not been modified because of the statistically not relevant variations.

In the epithelial cells of the EMR Community ($p < 0.05$), immune histochemical monitoring of the ovaries has shown substantial changes in Caspase-3 expressions. Hyperemia in uterine tissues was found in the EMR community. The EMR group was greatly improved by Caspase-3 and Caspase-8 ($p<0.001$). With the application of Vitamin C in ovarian and uterine tissues ($p<0.05$) Caspase-3 was substantially decreased. In the uterine tissues alone ($p<0.05$) Caspase-8 was greatly decreased.

These findings suggest that repeated exposure to EMR triggered changes in ovarian, fallopian and uterine tissues owing to oxidative damage to physiopathology's. Vitamin C will protect women's reproductive system from oxidative damage under the conditions of this study (Saygin et al., 2018).

The rate and number of deliveries by cesarean is directly associated with some of the maternal risks such as long surgery time, peripheral organ damage, need for intensive care, maternal death, bleeding and hysterectomy (Kaplanoglu, Bulbul, Kaplanoglu, & Bakacak2015). The mode of delivery is also associated with age such as chances of cesarean deliveries are most common at the age from 31-40. As the age increase, the chances of normal delivery or miscarriage enhance due to weak immunity. There are more complications at the time of delivery at the age from 21-30. Thus, it is clear that age is directly related with mode

of delivery as well as complications during delivery. The study showed that second mode of delivery depends on first mode for example, if a previous delivery mode of a woman was SVD than there are high chances of SVD for current delivery and vice versa (Rowlands, (2012). Thus, it is clear that the delivery modes highly depend on first delivery and women should go for SVD because there are less complication with SVD as compare to cesarean.

*n) Function of Menopause Oxidative Damage*

The role of oxidative stress in menopause has been determined by Sejal Doshi etcetera. The research addresses the idea of reproductive ageing that involves identifying menopause, its symptoms and the disorders predisposed to menopause. It will discuss the leading factors to menopause pathogenesis, with an emphasis on oxidative stress. This study would explicitly illustrate how oxidation stress is directly related to the decrease in oestrogen during reproductive ageing, in the form of free radically and antioxidant deficiency.

This paper will also address treatment strategies to reduce menopausal complications and hormones that can contribute to multiple disease processes. Options such as oestrogen treatment, supplemental antioxidants and dietary changes have been researched in order to determine their usefulness in treating and avoiding menopause symptoms and sequelae. PubMed and the National Library of Medicine have collected the bulk of the data in this study. While the bulk of references are original research papers, a handful of references are detailed evaluations (Doshi & Agarwal, 2013).

Kennare et.al conducted a study and compares the risks of second birth after first birth in cesarean and vaginal birth. In this study the data was collected from South Australian during the year of 1998 to 2003 and compare almost 2733 women who have vaginal first birth with the 8725 women who have cesarean first birth. The results of this study show that abnormalities due to cesarean are high after first birth and it may harm the mother and baby both. (Kennare 2010)

Silveiral et al. conducted a study to show a comparison of cesarean and vaginal birth deliveries. This study was conducted in Brazil in 2004 and all the mothers are investigated in hospitals during their stay in hospitals. Doctors and nurses asked from them about their previous family gestational history. The results of this study show that the overall rate of cesarean in Brazil is 45% in their government hospitals and 81% in private hospitals. This study shows that private hospitals have high rate of cesareans.

P Braveman et.al conuted a study to relate that how ethnicity depends on the cesarean. In this study he discussed that either race of women are dependent or not on cesarean delivery. It is a retrospective based study and this study is conducted in California in th year of 1991. This study shows that the chances of cesarean in black women are 24% high then the white women. The result of this study was that ethnicity is highly effect the cesarean but other social activities of the women are not affected and be a cause of cesarean. (Braveman, P., Egerter, S., Edmonston, F. 19950)

Adriant Grant conducted a study to show that how cesarean reduce the morbidity or death of premature birth but it may cause abortion or risk of maternal. In this study the Cochrane pregnancy and childbirth methods are used to investigate. In this study the data of 122 women are taken and check the maternal abnormalities in these women and their new born babies. The results shows that the babies of these women have less chances of respiratory distress syndrome and neonatal seizures and very few deaths occurred but the mothers are at high risks.(Grant, A 2001)

Richard et.al conducted a study to discuss the causes, trends and solution of huge cesarean cases. In this study it is also determines that the vaginal birth rate is decreased day by day because most of the women choose cesarean because they have no tendency to bear the labor pains during pregnancy. This study also shows that the some strategies are applied to reduce the cesarean cases and induce the labor pains so that vaginal birth can be enhanced. (Porreco, R. P.1996)

E.L conducted a study to discuss the psychological effect in emergency cesarean case ad vaginal birth case. This study shows that psychology has a great effect on the type of birth either vaginal or emergency cesarean. If they are already known that they have cesarean it impacts negative effect on the health of mother and baby but if its an emergency case then it doesn't have more negative impact on the mother health. The results show that an unplanned cesarean delivery has less negative impact on health. (Ryding, E. L., Wijma, K.1998)

Kiel conducted a study to show that how obesity in women can alter the pregnancy and mode of delivery. This is a cohort study in which data was collected of 120251 obese pregnant women to check that how obesity affect the pregnancy. The results of the data shows that if there is no extra abdominal weight is gain the pregnancy is not altered or affected in obese patient. (Kiel, D. W., Dodson, E. A., Artal, R., Boehmer, T. K.2007)

Projestine S Muganyizi et.al conducted a study to discuss that how different age groups pregnant women affected by their delivery. This study is conducted in tertiary hospital of Tanzania and discusses that different age groups has no major effect on the pregnancy outcomes. This study indicates that mothers of high ages have more chances of cesarean delivery and less age group have less chances of cesarean delivery.

o) *Protective Part of Vitamin E on Nickel Induced Oxidative Stress in Ovary of Female Reproductive System*

Mandava et al. carried out an analysis to establish the protective effect of vitamin E in the ovary of the female reproductive system on nickel and chromium mediated oxidative stress. In the present study, nickel chloride (niCl2) and potassium dichromate (K2Cr2O7; 5 mg/kg body weight) were identified in vivo to adult mice. Overall, in vivo, adult mice were found to have a diagnostic effect. The vitamin E protective function (2 mg/kg body weight) was also analysed in accordance with its combination. The level of lipid peroxides in the ovary has risen with nickel and/or chromium to the mouse, followed by a substantial reduction in the levels of protein, glutathione, complete ascorbic acid, dismutase and catalase of superoxide's.

The vitamin E supplement with NiCl2 + K2Cr2O7 decreased lipid peroxidation levels considerably and improved antioxidant status.The results of this study indicate that the safety of vitamin E from toxicity by avoiding lipid peroxidization and by shielding the anti-oxidant system in women's ovaries against nickel and/or chromium.

p) *Role of Reactive Oxygen Species in Female Reproduction*

Rizzo et al. carried out an analysis to determine the function of female breeding reactive oxygen species. Reactive oxygen molecules are the highly reactive oxidizing agents (ROS). Under aerobic conditions, cells offer ROS defense and a strong balance occurs under natural conditions between pro-oxidants and antioxidants. Oxidative stress happens, during which ROS accumulates and destroys the cells and organs, if the body is unable to remove ROS unnecessarily. In addition to the adverse effects, accumulation of evidence has shown the physiological impact of regulated and sufficient ROS levels.

Different experiments have verified the presence of ROS and transcripts in women's breeding tract. When ROS development is overcome by antioxidants, oxidative stress, which can endanger the anatomical and functional integrity of the genital tract, occurs. It deals with the major physiological and pathological roles played by ROS and its scavenging mechanisms inmultiple processes that engage in the primary physiological functions of the women's and domestic animals' reproductive tract. The role of oxidizers in many reproductive processes, such as follicular growth, ovarian steroidogenesis, ovulation, luteolytic, germ cell functions, pregnancy maintenance and starting parturition, is studied in particular.

q) *Implication of Oxidative Stress on Female Infertility*

Ashok Agarwal et al. showed a learning to determine the oxidative stress and its implication in the female infertility.Reactive oxygen species (ROS) play a significant role in gamete content modulation and gamete interaction. Spermatozoa and leukocytes contaminating ROS generation is inherent. Sperm, ovaries, eggs, and their environment are affected by ROS. Sperm membrane peroxidant damage is mediated by oxidative stress (OS), which causes nuclear DNA damage. ROS can modulate the sperm fertiliser ability. There is a wide variety of literature on OS and its working in male infertility and DNA damage and its effect on assisted reproductive techniques. Facts are obtained in the role of ROS in female reproduction.

In oocyte growth, ripening, follicular atresia, corpus luteum and luteolytic several animal and human studies have highlighted ROS' function. The precipitation mediated by the OS of reproductive pathologies in women is similar to the precipitation involving male infertility. OS affects the efficiency and the fertilization rates of the oocytes and embryos. In gamete activity modulation and efficient fertilization, ROS tends to production an significant role (Ramalho-Santos et al., 2009). In cultural media ROS may affect the production of post-fertilization, i.e.cleavage rate, blastocyst yield and efficiency (indicators of assisted reproduction outcomes).

Both natural and aided fertility are recorded to impact OS. The methods for antioxidants should be able to intercept extracellular as well as intracellular ROS. This analysis explores origins of ROS in media for the movement of IVF embryos and methods for OS control in in-vitro ripening of the oocytes, in-vitro cultivation and sperm preparation techniques.

In the aetiology of female reproductive disorders, the complex link between cytokines and oxidative stress is discussed. Cell regulation of Angiogenesis is important for follicular development, separating of dogmas and for embryonic growth of the formation of corpus lute. Techniques for controlling oxidative stress and improving fertility are both natural and supportive. Early pre-eclampsia preventive strategies are discussed. The pre-eclampsia avoidance illustrates tests for the discovery of vitamin C and vitamin E intake in combination treatment.

In some trials, high levels of antioxidant additives were examined in sexual breeding. But before doctors prescribe antioxidant to demonstrate the effectiveness of antioxidant supplementation in women's replicative disorders, randomized controlled trials with adequate intensity are needed. Duration studies may help to delineate the aetiology of certain disorders, such as preeclampsia for female reproduction by means of serial test measurements for oxidative stress biomarkers (Agarwal et al., 2005).

r) *Anti-Oxidant Nutrient and Lead Toxicity*

The analysis of the antioxidant nutrient as well as the lead toxicity in mammalian cells was carried out by Ping-Chi et al. Lead-induced oxidative stress leads to

pathogenesis of lead poisoning in mammalian cells to interrupt the fragile prooxidant/antioxidant balance. After lead treatment in in vitro experiments, production of reactive oxygen species (ROS) is increased. Studies in vivo indicate that lead toxicity contributes to ROS production and modification of the protection mechanism for antioxidants in animals and employees exposed to jobs. The mechanism for oxidative stress triggered by circuitry involves the impact of plumbing on membrane, DNA and cell protection antioxidant systems.

In epidemiological and animal research, there are differing responses from low to elevated levels of plum sensitivity to oxidative stress at various target sites such as lung, blood vessels, testes, sperm, liver and brain. The beneficial effect of antioxidant nutrients by exogenous enrichment of antioxidant molecules may thus be correlated with reducing the capacity for lead to interfere with essential biological molecules and causing oxidative harm or enhancing cell antioxidant defenses. Although a number of studies have researched the use of antioxidants to avoid lead toxicities, the functions of antioxidant nutrients are not entirely apparent by the re-equalization of the degraded prooxidant/antioxidant ratio. The analysis addresses their beneficial function in lead-induced oxidation stress by discussing the antioxidant nutrients namely, vitamin E, vitamin C, vitamin B6, β-carotene, zinc and selenium (Hsu & Guo, 2002).

It also deals with female SA infertility and how it influences the effects of aided breeding techniques. The paper explores in depth the role of oxidation stress in conditions such as abortion, preeclampsia, hydatidiform mole, foetal embryopathy. The thesis also addresses the increased role of nitrogen oxide species in reproduction by women in the literature. It covers the participation of nitrial oxide Dravidian in endometrial as well as ovarian structure planning, etiopathology of endometriosis, support of vaginal stimuli, initiation of work and maturation of the cervix.

Junichi Fuji et al. (2005) conducted a study to explore the basic roles of reactive oxygen species as well as protective mechanism in the female reproductive system. This study explored that controlled oxidation such as disulphide bind present at the nuclei of sperm during the ovulation imparts an important and basic role in female reproductive system. The presence of high oxygen causes oxidative stress that results into the dysfunction of all process of reproductive system. The presence of anti-oxidation reactions reduced the level of reactive oxygen species and imparts an important role in maintaining the quality of gametes as well as reproduction system. The presence of oxidative enzymes such as superoxide dismutase as well as peroxide imparts a significant role in elimination of these oxidative stress. The redox reactions present in female reproductive system are comprised of two main reactive agents such as glutathione as well as thioredoxin that reduced the level of oxidized molecule and also reduced the oxidative stress in female reproductive system. Thus, this study determined that antioxidants as well as redox enzymes imparts an important role in providing protection to gametes as well as gametes in female reproductive system.

s) *Role of Oxidative Stress and Antioxidants in Assisted Reproduction*

Sajal Gupta et al. (2010) conducted a study to measure the role of oxidative stress and antioxidants in assisted reproduction. Oxidative stress correlates to an increased rate of failure to achieve fertilization and pregnancy in assisted reproductive procedures. Many studies have been carried out to elucidate oxidative stress sources for ART and therapies to overcome the unfavourable effects of IVF and ICSI. Oxidative stress sources were determined in this context. This article addresses the use of metabolomics as a unique, non-invasive tool for evaluating oxidative stress precisely and efficiently. The purpose of this study was to examine the current literature on the impact of several therapies, including the use of IVF culture supplements antioxidants in the field of fertilization well as rates of pregnancy in the subdertile patients undergoing ART.

Examination by Pubmed and the Cochrane databases of recent publications Outcome: Oxidative stress is linked to the unfavourable effects of ART. The IVF/ICSI is well-established in literature both exogenous and endogenous sources of reagent oxygen species. The exposure of gametes to endogenous sources of oxidative stress has been minimised by ICSI, compared with the IVF. Strategies to minimise oxidative stress sources within a randomized ART environment include limiting visible / close UV exposure, adding metal chelators to cultivation media, maintaining low environmental oxygen tension and using antioxidant treatment. The vitamin C, vitamin E and melatonin anti-oxidant addition of culture media has been researched and inconsistent findings have been produced. With the acceptance and practise of oral antioxidant supplements in male patients, there is no consensus on the usefulness of ART supplementation in females, vitamin E and melatonin. Further research into the efficacy and safety of antioxidant supplementation of culture medium and patients and the necessity for determination of the dosages required to promote fertilization and pregnancy are necessary in randomized controlled trials.

## V. Conclusion

It is concluded that oxidative free radicals present but the imbalance between these radicals leads into the oxidative stress. There are two ways to reduce the oxidative stress either by using enzymes or by vitamins as both act as the antioxidants. This study

explained that vitamin E and vitamin C imparts an important as antioxidant in the prevention of the side effects of oxidative stress. Due to the metabolic rate and the growth in mitochondrial activities Placenta may be the primary source of OS. Placental tissues have low concentrations and key antioxidant function during the first quarter, including catalase, glutathione peroxidase and superoxide dismutase. This condition will cause oxygen-mediated damage to the embryonic trophoblast cells.

Despite the gains made in the field of ART, antioxidant therapy has been a matter for much discussion and has been used to reduce the infertility burden by improving IVF and ICSI procedures. Although current information literature makes no definite conclusions about whether the specific antioxidant supplementation of patients with infertility and the culture media used for the use of ART will increase the success of the ART, important evidence suggests that this is a well-known contributor to ART failure and has the potential to fight oxidative stress. There is no question that an underlying relationship exists between OS and fertilization and possible IVF pregnancy. Thus, this study concluded that vitamin C and vitamin E imparts an important role in female reproductive system as an antioxidant.

*Abbreviations*

CVD Cardiovascular Disorders
DNA Deoxyribonucleic Acid
FA Formaldehyde
GPx Glutathione Peroxidase
LPO Lipid Peroxidation
NOS Nitrogen Species Reactive
OS Oxidative Stress
PUFAs Polyunsaturated Fatty Acid
ROS Reactive Oxygen
SOD Superoxidase Dismutase
VPA Valproic acid

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# Global Journals Guidelines Handbook 2022

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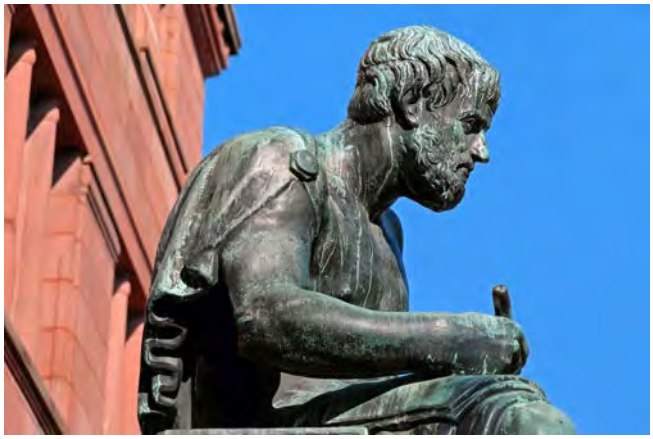
# Memberships

## 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.

# Benefit

## 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

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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

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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,
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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

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Career | Credibility | Financial

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Exclusive


## Publishing Articles & Books

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Exclusive | Financial

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## 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.

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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


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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

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

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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:

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- Findings
- Writings
- Diagrams
- Graphs
- Illustrations
- Lectures

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

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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.

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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.

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## 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.

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***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<br>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

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