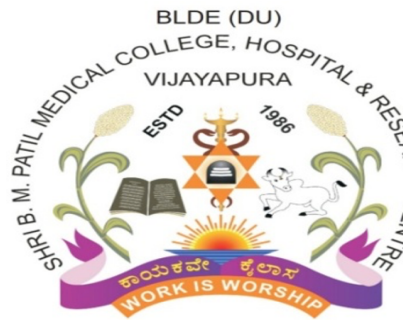


**“EVALUATION OF miRNA – 210 AS PROGNOSTIC BIOMARKER
OF PRE-ECLAMPSIA - A CASE – CONTROL STUDY”**

BY

DR. KOTA SAI MEGHANA



Dissertation submitted to

B.L.D.E (DEEMED TO BE UNIVERSITY) VIJAYAPURA

In partial fulfilment of requirements for the award of the degree of

MASTER OF SURGERY

OBSTETRICS AND GYNAECOLOGY

UNDER THE GUIDANCE OF

DR. RAJASRI G YALIWAL

MBBS, MS (OBG) FICOG

PROFESSOR

DEPARTMENT OF OBSTETRICS AND GYNAECOLOGY

B.L.D.E (DEEMED TO BE UNIVERSITY)

SHRI B.M. PATIL MEDICAL COLLEGE, HOSPITAL AND RESEARCH

CENTER, VIJAYAPURA-586103, KARNATAKA

2025

**SHRI B.M. PATIL MEDICAL COLLEGE HOSPITAL & RESEARCH
CENTRE (B.L.D.E. Deemed to be University), VIJAYAPURA**

DECLARATION BY THE CANDIDATE

I hereby declare that this dissertation titled **“EVALUATION OF miRNA – 210 AS PROGNOSTIC BIOMARKER OF PRE-ECLAMPSIA - A CASE – CONTROL STUDY”** is a bonafide and genuine research work carried out by me under the supervision and guidance of Dr. Rajasri G Yaliwal, Professor, Department of Obstetrics and Gynecology, Shri B. M. Patil Medical College and Research Centre, Vijayapura.



Dr. KOTA SAI MEGHANA
Post Graduate Resident
Department of Obstetrics and Gynaecology
BLDE (Deemed to be University)
Shri B.M. Patil Medical College,
Hospital & Research Centre, Vijayapura

Date: 29/03/2025

Place: Vijayapura

**SHRI B.M. PATIL MEDICAL COLLEGE HOSPITAL & RESEARCH
CENTRE (B.L.D.E. Deemed to be University), VIJAYAPURA**

CERTIFICATE BY THE GUIDE

This is to certify that the dissertation titled - **“EVALUATION OF miRNA – 210 AS PROGNOSTIC BIOMARKER OF PRE-ECLAMPSIA - A CASE – CONTROL STUDY”** is a bonafide and genuine research work done by **Dr KOTA SAI MEGHANA** in partial fulfillment of the requirement for the degree of Master of Surgery in Obstetrics and Gynecology.



Dr. RAJASRI G YALIWAL

Professor

Department Of Obstetrics and Gynaecology

BLDE (Deemed to be University)

Shri B.M. Patil Medical College,

Hospital & Research Centre, Vijayapura

Date: 29/03/2025

Place: Vijayapura

**SHRI B.M. PATIL MEDICAL COLLEGE HOSPITAL & RESEARCH
CENTRE (B.L.D.E. Deemed to be University), VIJAYAPURA**

CERTIFICATE BY THE CO-GUIDE

This is to certify that the dissertation titled - **“EVALUATION OF miRNA – 210 AS PROGNOSTIC BIOMARKER OF PRE-ECLAMPSIA - A CASE – CONTROL STUDY”** is a bonafide and genuine research work done by **Dr KOTA SAI MEGHANA** in partial fulfillment of the requirement for the degree of Master of Surgery in Obstetrics and Gynecology.

Dr G S KADAKOL

Dr. GURUSHANTAPPA S KADAKOL (Msc., PhD)

Assistant Professor

Genetics Laboratory And

School of Applied Sciences and Technology

BLDE (Deemed to be University)

Shri B.M. Patil Medical College,

Hospital & Research Centre, Vijayapura

Date: 29/03/2025

Place: Vijayapura

**SHRI B.M. PATIL MEDICAL COLLEGE HOSPITAL & RESEARCH
CENTRE (B.L.D.E. Deemed to be University), VIJAYAPURA**

ENDORSEMENT BY THE HEAD OF DEPARTMENT

This is to certify that this dissertation titled **“EVALUATION OF miRNA – 210 AS PROGNOSTIC BIOMARKER OF PRE-ECLAMPSIA - A CASE – CONTROL STUDY”** is a bonafide work done by Dr. KOTA SAI MEGHANA, under overall guidance and supervision of **Dr. RAJASRI G YALIWAL**, Professor, Department of Obstetrics and Gynecology, Shri B.M. Patil Medical College Hospital and Research Centre, in partial fulfillment of the requirement for the degree of M. S. in Obstetrics and Gynecology, examination to be held in 2025.



Dr. (Prof.) SHAILAJA R BIDRI
Professor and Head of the Department
Department of Obstetrics & Gynaecology
BLDE (Deemed to be University)
Shri B.M. Patil Medical College,
Hospital & Research Centre, Vijayapura

Date: 29/03/2025

Place: Vijayapura

**SHRI B.M. PATIL MEDICAL COLLEGE HOSPITAL & RESEARCH
CENTRE (B.L.D.E. Deemed to be University), VIJAYAPURA**

ENDORSEMENT BY THE PRINCIPAL

This is to certify that the dissertation titled **“EVALUATION OF miRNA – 210 AS PROGNOSTIC BIOMARKER OF PRE-ECLAMPSIA - A CASE – CONTROL STUDY”** is a bonafide research work done by **Dr. KOTA SAI MEGHANA** under the guidance of **Dr. RAJASRI G YALIWAL**, Professor, Department of Obstetrics and Gynaecology, Shri B M Patil Medical College Hospital & Research Centre, Vijayapura, Karnataka in partial fulfilment of the requirement for the degree of Doctor M.S in Obstetrics and Gynaecology, examination to be held in 2025.



Dr. ARAVIND V PATIL

Principal

BLDE (Deemed to be University)

Shri B.M. Patil Medical College,

Hospital & Research Centre, Vijayapura

Date: 29/03/2025

Place: Vijayapura

**SHRI B.M. PATIL MEDICAL COLLEGE HOSPITAL & RESEARCH
CENTRE (B.L.D.E. Deemed to be University), VIJAYAPURA**

COPYRIGHT

DECLARATION BY THE CANDIDATE

I hereby declare that the Shri B. M. Patil Medical College Hospital and Research Centre, B.L.D.E (DEEMED TO BE UNIVERSITY), Vijayapura, Karnataka, India, shall have the rights to preserve, use, and disseminate this dissertation/thesis in print or electronic format for academic / research purposes.



Dr. KOTA SAI MEGHANA

Date: 29/03/2025

Place: Vijayapura

ACKNOWLEDGEMENT

I am eternally grateful to God for the strength, wisdom, and perseverance. He has given me strength and encouragement throughout all the challenging moments of completing this dissertation. It gives me great pleasure to offer my profound appreciation to everyone who has helped me, directly or indirectly, to study the vast expanse of knowledge. I take this opportunity to extend my sincere gratitude and wholehearted thanks to all those who helped me to complete this dissertation.

First and foremost, I am deeply honored to express my profound gratitude to my guide and esteemed teacher, **Dr. RAJASRI G YALI WAL M.S(OBG), FICOG, Professor, Department of OBG**, Shri B.M. Patil Medical College, Vijayapura, for her invaluable guidance, unwavering support and insightful suggestions throughout my dissertation journey. Her deep commitment to academic excellence and meticulous attention to detail have significantly shaped this dissertation. Undoubtedly, this has provided me with a solid understanding of in the field of Obstetrics and Gynaecology, allowing me to complete my dissertation.

I extend my sincere thanks to my co-guide, **Dr. GURUSHANTAPPA S KADAKOL** (Msc., PhD) Assistant Professor, Genetics Laboratory And School of Applied Sciences and Technology, BLDE (Deemed to be University) for his for his continuous assistance and aid in genetic analysis and research. His contributions have significantly enhanced the quality of this research.

I am deeply indebted to **Dr. SHAILAJA R BIDRI**, M.D. D.G.O., Obstetrics & Gynaecology, Professor and Head of the Department of Obstetrics and Gynaecology, for imparting a wealth of information and life lessons that I will keep

with me in all parts of my personal and professional life. Thank you, Madam, for the invaluable lessons in patient care and hospital procedures that have helped to complete this project.

I sincerely thank my esteemed teachers, **Dr.S.R Mudanur, Dr.Neelamma Patil, Dr. Aruna M Biradar, Dr. Shobha Shiragur, Dr. Shreedevi Kori** for imparting their wisdom in every aspect and providing a stimulating academic environment. Your knowledge and dedication have inspired me greatly.

I express my gratitude to **Dr. Aravind V. Patil, Principal and Dr. Rajesh Honnutagi, Medical Superintendent, of Shri. B.M. Patil Medical College Hospital and Research Centre, Vijayapura**, for permitting me to conduct and utilize resources in completing my work.

My sincere thanks to all my patients who willingly consented themselves to be a part of this study. My heartfelt thanks to all my co-postgraduates, **Dr Lavanya Paleti, Dr Keerthi Chowdary, Dr. Yamini Magnati** and juniors for their support. A special word of gratitude goes to **Mr. Ajay Kumar Statistician**, Shri. B.M. Patil Medical College, Vijayapura, for his aid and invaluable help concerning the statistical work for this study.

My heartfelt thanks go to my beloved best friends, **Dr SUSHMA REDDY, Dr AISHWARYA CHOWDARY** for their encouragement, moral support and for always keeping me grounded. This would have been a much more difficult feat without you all. Thank you all for your unwavering support and for reminding me to take breaks and have fun when I've been stressed out.

I want to acknowledge the invaluable role my family plays in my life and extend my heartfelt thanks. I am deeply grateful to my parents, **KOTA RAVI CHANDRA and KOTA MADHAVI** and my grandparents **GHANTA MADHUSUDHAN RAO and GHANTA PARVATHI**, for their unconditional love and encouragement, without which I wouldn't be at this point, and being a constant source of strength and inspiration, reminding me of the value of perseverance. I am particularly grateful to my parents for their unwavering support, both emotionally and financially, which made this dissertation possible.

I am truly fortunate to have the support of my parents, and I dedicate this dissertation to them.

I finally bow my head in respect before The Almighty and my Alma Mater, who have protected me and shown me the right path through this gratifying task.

Dr. KOTA SAI MEGHANA
Post Graduate Resident
Department of Obstetrics and Gynaecology
BLDE (Deemed to be University)
Shri B.M. Patil Medical College,
Hospital & Research Centre, Vijayapura

Date: 29/03/2025

Place: Vijayapura

ABBREVIATIONS

<i>ABBREVIATION</i>	<i>EXPANSION</i>
<i>WHO</i>	World Health Organization
<i>PE</i>	Pre-eclampsia
<i>ISSHP</i>	International Society for the Study of Hypertension in Pregnancy
<i>FIGO</i>	International Federation of Gynecology and Obstetrics
<i>sFLT-1</i>	Soluble FMS-like Tyrosine Kinase-1
<i>sENG</i>	Soluble Endoglin
<i>IUGR</i>	Intrauterine Growth Restriction
<i>ROS</i>	Reactive Oxygen Species
<i>VEGF</i>	Vascular Endothelial Growth Factor
<i>PIGF</i>	Placental Growth Factor
<i>TGF - β</i>	Transforming Growth Factor-Beta
<i>NO</i>	Nitric Oxide
<i>HIF</i>	Hypoxia-Inducible Factor
<i>HELLP</i>	Hemolysis, elevated liver enzymes, and low platelets Syndrome
<i>IUFD</i>	Intrauterine Fetal Demise
<i>NST</i>	Nonstress Test
<i>FHR</i>	Fetal Heart Rate
<i>NICU</i>	Neonatal Intensive Care Unit
<i>IQ</i>	Intelligence Quotient
<i>PHOENIX</i>	Planned Early Delivery Or Expectant Management For Late Preterm Pre-Eclampsia

<i>ACOG</i>	American College of Obstetricians and Gynecologists
<i>NICE</i>	National Institute for Health and Care Excellence
<i>PAPP-A</i>	Pregnancy-Associated Plasma Protein A
<i>DNA</i>	Deoxyribonucleic acid
<i>NCRNA</i>	Non-coding RNA
<i>PP13</i>	Placental Protein 13
<i>miRNA</i>	MicroRNA
<i>piRNA</i>	Piwi-interacting RNA
<i>siRNA</i>	Small interfering RNA
<i>PAR</i>	Promoter-Associated RNA
<i>PASR</i>	Promoter-Associated Small RNA
<i>TSSa</i>	Transcription Start Site-Associated RNA
<i>tiRNA</i>	Transcription Initiation RNA
<i>PROMPT</i>	Promoter Upstream Transcripts
<i>RISC</i>	RNA-Induced Silencing Complex
<i>eRNA</i>	Enhancer RNA
<i>ssRNA</i>	Strand-Specific RNA Sequencing
<i>dsRNA</i>	Double-stranded RNA
<i>lincRNA</i>	Long Intervening Noncoding RNA
<i>Pri-miRNA</i>	Primary miRNA
<i>UTR</i>	Untranslated Region
<i>TRBP</i>	Transactivation Response RNA-Binding Protein
<i>AGO2-RISCs</i>	Argonaute RISC Catalytic Component 2
<i>PACT</i>	Protein Activator of Interferon Induced Protein Kinase
<i>ADAR</i>	Adenosine Deaminases Acting on RNA

<i>qRT-PCR</i>	Quantitative Reverse Transcription Polymerase Chain Reaction
<i>NGS</i>	Next-Generation Sequencing
<i>TET1</i>	Ten-Eleven Translocation 1
<i>KCNMB1</i>	Potassium Calcium-Activated Channel Subfamily M Regulatory Beta Subunit 1
<i>RYR2</i>	Ryanodine Receptor 2
<i>STOCS</i>	Spontaneous Transient Outward Currents
<i>NF-κB</i>	Nuclear Factor kappa-light-chain-enhancer of activated B cells
<i>ceRNA</i>	Competing Endogenous RNA
<i>KCMF1</i>	Potassium Channel Modulatory Factor 1
<i>MAPK</i>	Mitogen-Activated Protein Kinase
<i>THSD7A</i>	Thrombospondin Type I Domain Containing 7A
<i>HOXA9</i>	Homeobox A9
<i>EFNA3</i>	Ephrin A3
<i>HTR8/SVneo</i>	Human Trophoblast Cell Line Derived From First-Trimester Placental Cells
<i>ISCU</i>	Iron-Sulfur Cluster Assembly Enzyme
<i>ACVR1B-APC</i>	Activin Receptor Type-1B
<i>CDK10-E2F3</i>	Cyclin dependent kinase 10 Early region 2 binding factor Transcription Factor 3
<i>SERTAD2</i>	SERTA Domain Containing 2
<i>ELK3-HOXA3</i>	ETS Transcription Factor Homeobox A3
<i>M1BI-NPTX1</i>	Neuronal Pentraxin 1

<i>ACVR1B-BDNF</i>	Activin A receptor type 1B - Brain-Derived Neurotrophic Factor
<i>ABCB9</i>	ATP Binding Cassette Subfamily B Member 9
<i>TNPO1</i>	Transportin 1
<i>CLASP2-</i>	Cytoplasmic Linker Associated Protein 2- MAM Domain–
<i>MDGA1</i>	Containing Glycosylphosphatidyl
<i>P4HB-PTPN1</i>	Prolyl 4-Hydroxylase Subunit Beta - Protein Tyrosine Phosphatase Non-Receptor Type 1
<i>NCAM1</i>	Neural Cell Adhesion Molecule 1
<i>SMCHD1</i>	Structural Maintenance of Chromosomes Flexible Hinge Domain Containing 1
<i>XIST</i>	X-Inactive Specific Transcript
<i>CDH9</i>	Cadherin 9
<i>CBX1</i>	Chromobox Protein Homolog 1
<i>TWIST</i>	Twist Family BHLH Transcription Factor 1
<i>ex-MIRNA</i>	Extracellular miRNA
<i>SMD</i>	Standardized Mean Difference
<i>HDP</i>	Hypertensive Disorders of Pregnancy
<i>AUC</i>	Area Under Curve
<i>SBP</i>	Systolic Blood Pressure
<i>DBP</i>	Dystolic Blood Pressure
<i>MABP</i>	Mean Arterial Blood Pressure
<i>PTT</i>	Partial Thromboplastin Time
<i>SGOT</i>	Serum Glutamic Oxaloacetic Transaminase
<i>SGPT</i>	Serum Glutamic Pyruvic Transaminase
<i>TSB</i>	Total Serum Bilirubin

<i>ALP</i>	Alkaline Phosphatase
<i>MCA</i>	Middle Cerebral Artery
<i>UA</i>	Umbilical Artery
<i>INR</i>	International Normalised Ratio
<i>BSUA</i>	Bedside Urine Albumin
<i>FGR</i>	Fetal Growth Restriction
<i>LSCS</i>	Lower Segment Caesarean Section
<i>NVD</i>	Normal Vaginal Delivery
<i>APH</i>	Antepartum Haemorrhage
<i>TOLAC</i>	Trial of Labor After Cesarean
<i>CPD</i>	Cephalopelvic Disproportion
<i>PPV</i>	Positive Predictive Value
<i>NPV</i>	Negative Predictive Value

TABLE OF CONTENTS

S.No	CONTENT	PAGE No
1	INTRODUCTION	24
2	AIMS AND OBJECTIVE	28
3	REVIEW OF LITERATURE	29
4	METHODOLOGY	73
5	RESULTS	82
6	DISCUSSION	122
7	SUMMARY	133
8	CONCLUSION	135
10	BIBIOGRAPHY	137
11	ANNEXURES	
	I - INFORMED CONSENT	152
	II - PROFORMA	156
	III - ETHICAL CLEARANCE	159
	IV - MASTER CHART	161

LIST OF FIGURES

FIGURE No.	DESCRIPTION	PAGE No.
FIGURE 1	Two-phase pathophysiology of PE.	31
FIGURE 2	Pathogenesis of PE	32
FIGURE 3	Sources and types of biomarkers that could be analyzed for preeclampsia assessment	35
FIGURE 4	Mechanism of ncRNAs in PE	44
FIGURE 5	Conventional pathway of miRNA biogenesis	49
FIGURE 6	Potential biomarkers used for predicting both early and preterm cases of PE	52
FIGURE 7	Various miRNAs involved in pathogenesis (Stage 1 & 2) of PE	55
FIGURE 8	miRNA-210 under hypoxic conditions repress spontaneous transient outward currents in uterine arteries	56
FIGURE 9	Demonstration of ceRNAs composed of lncRNAs and circRNAs guide microRNA targets to achieve competitive endogenous RNA control	57
FIGURE 10	Overexpression of miRNA-210 causing PE development	58

FIGURE 11	Summary of cellular processes which miRNA-210 modifies through direct and indirect influences	61
FIGURE 12	Total RNA	77
FIGURE 13	Flowchart of participant recruitment in case-control study	83
FIGURE 14	Bar graph showing distribution of study population based on age	89
FIGURE 15	Bar graph showing distribution of weight of the study population	91
FIGURE 16	Bar graph showing distribution of period of gestation among the study population	92
FIGURE 17	Bar graph showing distribution of parity status among the study population	94
FIGURE 18	Pie chart showing distribution of Maternal complications in Group I	110
FIGURE 19	Pie chart showing distribution of Maternal complications in Group II	111
FIGURE 20	Pie chart showing distribution of Indications For Caesarean section in Group 1	114
FIGURE 21	Pie chart showing distribution of Indications For Caesarean section in Group 1	115

FIGURE 22	Pie chart showing distribution of Sex of baby among study population I & II	117
FIGURE 23	ROC Curve of miRNA-210 in evaluation of PE	119
FIGURE 24	Bar graph showing miRNA - 210 in both study groups	120
FIGURE 25	Line Diagram showing comparison of miRNA-210 in both study groups	121

LIST OF TABLES

Table No.	DESCRIPTION	Page No.
Table 1	Table showing perinatal and neonatal complications of pre-eclampsia which have short and long term	34
Table 2	Current tests used for evaluation of pre-eclampsia	38
Table 3	Table showing types of NcRNAs and their biological roles	43
Table 4	Table showing several miRNAs involved in pre-eclampsia	53
Table 5	Table showing poly(A)/cDNA synthesis reaction	78
Table 6	Table showing sample qPCR reaction	79
Table 7	Table showing U6 qPCR reaction	79
Table 8	Table showing quantification of RNA by multimode reader	84
Table 9	Table showing distribution of study population based on age	86
Table 10	Table showing distribution of study population based on weight	90
Table 11	Table showing distribution of study population based on period of gestation	91
Table 12	Table showing distribution of study population based on parity status	92
Table 13	Table showing comparison of clinical and lab data between the studied groups	93

Table 14	Table showing comparison of clinical and lab data between the studied groups	95
Table 15	Table showing fetal growth parameters in both study groups	96
Table 16	Table showing correlation coefficient (r) between miRNA-210 and study groups	98
Table 17	Table showing analysis between study groups using Pearson's chi-squared test	100
Table 18	Table showing miRNA-210 in Group 1 (51 cases) in association with maternal, neonatal complications, duration of NICU stay and birth weight	101
Table 19	Table showing miRNA-210 in Group 1 (51 cases) in association with maternal, neonatal complications, duration of NICU stay and birth weight	105
Table 20	Table showing miRNA-210 in Group 1 (51 cases) in association with maternal, neonatal complications, duration of NICU stay and birth weight	106
Table 21	Table showing miRNA-210 ($2^{-\Delta\Delta Cq}$ expression) levels via RT-PCR in both study groups	107
Table 22	Table showing miRNA-210 in study groups	118

ABSTRACT

BACKGROUND: Pre-eclampsia (PE) is a significant disorder impacting 2%-8% of pregnancies globally. Nevertheless, the key molecular etiology of this disease has predominantly remained unclear. Recently published studies have suggested the potential significance of miRNAs, particularly miRNA-210, in the etiology of PE. This study aims to evaluate the role of miRNA-210 as a novel biomarker for predicting pre-eclampsia (PE).

OBJECTIVE: This study objective is to assess the level of miRNA 210 in pre-eclampsia (PE) and to evaluate its role in the diagnosis and prognosis of the disease.

MATERIALS AND METHODS: This was a case - control study, conducted from April 2023 - February 2025, carried out in pre- eclamptic women and normotensive women, who got admitted to the Department of OBSTERTICS & GYNAECOLOGY in B.L.D.E. (DEEMED TO BE UNIVERSITY) Shri B.M. Patil Medical College Hospital and Research Centre, Vijayapura. Women who fulfilled the inclusion criteria were enrolled in the study after taking written and informed consent. The study included 102 pregnant women, categorized into two groups: Group 1 consisted of 51 women with pre-eclampsia as cases, while Group 2 consisted of 51 normotensive pregnant women matched age with ± 5 years, gestational period with ± 1 week, and Obstetric score, were included as the control group. All women participating in this study had comprehensive history taking, a full clinical examination, and laboratory tests, which included complete blood count (CBC), Coagulation Profile, Renal Function Test (RFT), Liver Function Test (LFT), proteinuria, and miRNA-210 gene expression analysis through RT-PCR. A sample

of peripheral venous blood was taken on admission and submitted for genetic analysis. After the genetic analysis, the study's parameters were compared. Maternal and neonatal outcome were also observed.

RESULTS: Patients with PE showed a highly significantly increase in serum miRNA-210 (*p value* < 0.001) compared to control group. miRNA- 210 has highly significant positive correlation with Systolic blood pressure, Diastolic blood pressure, MABP, serum Protein, serum Albumin, serum Uric acid, serum ALP. However, no significant correlation was found with Hb%, platelet count, INR and serum creatinine. At a cutoff value of 9.63 -fold change, the serum miRNA-210 levels shows 100% sensitivity along with 96.1% specificity at while PPV and NPV values were 96.2% and 100%, respectively.

CONCLUSION: The expression of miRNA-210 is elevated in women with pre-eclampsia, with higher levels seen in the pre-eclamptic women compared to the normotensive pregnant women. Thus, serum miRNA-210 may serve as a diagnostic and predictive biomarker in patients with pre-eclampsia, as well as assist in the understanding its etiology.

Key Words: miRNA-210, Pre-eclampsia, biomarker, RT PCR

INTRODUCTION

The World Health Organization (WHO) provides published recommendations which define pre-eclampsia as a serious obstetrical condition with multiple contributing factors. Pre-eclampsia (PE) develops in normotensive pregnant individuals who develop blood pressure reaching $\geq 140/90$ mm Hg combined with proteinuria exceeding 0.3 gm in 24 hours urine collection or $\geq 1+$ by dipstick beyond 20 weeks of gestation. ^[1]

Various hypotheses exist to explain PE's developmental process. All theories share one central principle based on vascular elements that trigger endothelial damage or cause vascular spasm. ^[2]

Several non-coding RNA molecules (ncRNAs) serve a role in the development of pregnancy disorders. miRNA-210 released from the placenta becomes a primary factor for trophoblastic endothelial vascular damage when hypoxic conditions develop in pre-eclampsia. The regulatory functions of miRNA-210 appear to influence cell division most significantly as well as DNA damage responses and mitochondrial metabolism and angiogenesis activities.

Studies showed that oxidative stress triggers hypoxia-dependent gene expression regulation mechanisms within trophoblast cells at the molecular level. Exosomes carry different microRNAs with some placental-origin microRNAs serving as accessible biomarkers for pre-eclampsia development. ^[3]

miRNA-210 belongs to a group of hypoxia-inducing microRNAs known as hypoxia-miRs. Many research studies indicate that hypoxic tissue contains higher levels of miRNA 210 which occurs through HIF dependent as well as HIF independent mechanisms. Oxygen depletion stabilizes HIFs heterodimers while it enhances nuclear gene expression through mechanisms which activate miRNA-210 transcription. Subunit HIF-1 α identifies and binds directly with a specific HRE (hypoxia responsive element) found within the proximal region of the miRNA-210 promoter. ^[4]

Under hypoxic conditions miRNA-210 shows elevated expression levels while elevated miRNA-210 levels may function as a modulator of mitochondrial dysfunction in PE. miRNA-210 functions as a key regulator of placental mitochondrial performance in patients who develop PE. ^[5]

Research shows that circulating miRNAs demonstrate as potential biomarker indicator of different human physiological conditions and diseases. A significant characteristic of miRNAs exists in their consistent presence within body fluids especially serum thus enabling minimal-invasive collection of samples for subsequent study. Placenta serve as the primary origin of miRNA-210 detected in pregnant women's serum yet it is crucial to consider that damaged endothelial cells might also produce miRNA-210 in serum. The stability of miRNA-210 in body fluids and serum allows it to function as a promising biomarker for pre-eclampsia development during pregnancy assessment. ^[4]

This case-control research aims to evaluate circulatory miRNA-210 functionality as an approach to non-invasive biomarker prediction of PE for high-risk pregnant women.

NEED FOR STUDY

Preeclampsia (PE) establishes itself as one of the most dangerous pregnancy complication which also emerges as a major source of maternal and neonatal mortality and morbidity. Thus, screening enables improved monitoring and management procedures allowing early detection of complications affecting pregnant individuals along with their neonates. The availability of specific diagnostic and imaging tools keeps advancing but regulatory protocols for their wide adoption have not been fully established making them ineligible for standard medical practice. The systemic development of disease starts with biochemical processes therefore focusing on established and emerging biomarkers related to preeclampsia through point-of-care screening approaches to minimize its burden.

The cellular importance of miRNA-210 biogenesis proves to be a superior choice for pre-eclampsia prognostic evaluations and future therapeutic approaches. ^[4]

AIMS AND OBJECTIVE

AIM:

Evaluation of miRNA - 210 as a Prognostic Biomarker in Pre-Eclampsia.

OBJECTIVE:

- ⇒ To detect and study miRNA-210 upregulation in the maternal serum of pre-eclamptic patients and compare it with normotensive pregnant women.

- ⇒ To correlate maternal outcome and neonatal outcome with miRNA - 210 expression levels.

REVIEW OF LITERATURE

Pre-eclampsia (PE) affects 2%-8% of pregnant women as a multisystem disorder which leads to the highest morbidity and mortality rates for both maternal and neonate especially when detected in early onset cases. [4,6,7,8] This condition every year leads to the mortality of around 76,000 women and 500,000 babies all over the world. [9] The risk of developing preeclampsia remains higher among women in low-resource nations than women in high-resource nations.

DEFINITION OF PRE-ECLAMPSIA:

Recent times have broadened the definition of PE. [11-14]

A previously normotensive woman develops PE when hypertension along with new-onset condition(s) appear after 20 weeks of pregnancy. The following conditions represented as one or more criteria to PE after 20 weeks of pregnancy (By FIGO, 2019): [10]

- ⇒ Proteinuria (i.e., ≥ 1 + by dipstick, ≥ 300 mg/24 hours, or ≥ 30 mg/mol protein: creatinine ratio)

- ⇒ Additionally, maternal organ dysfunction may include: acute kidney injury (creatinine ≥ 90 $\mu\text{mol/L}$ or 1mg/dL); hepatic involvement (with elevated transaminases, such as alanine aminotransferase or aspartate aminotransferase >40 IU/L) with or without right upper quadrant or epigastric abdominal pain; neurological complications (e.g., eclampsia, altered mental status, blindness, stroke, headaches, and visual changes; or hematological complications (such

as thrombocytopenia with a platelet count $<150,000/\mu\text{L}$, disseminated intravascular coagulation, or hemolysis).

⇒ Uteroplacental insufficiency, includes fetus-related conditions like growth restriction combined with abnormal umbilical artery Doppler changes or stillbirth. ^[10]

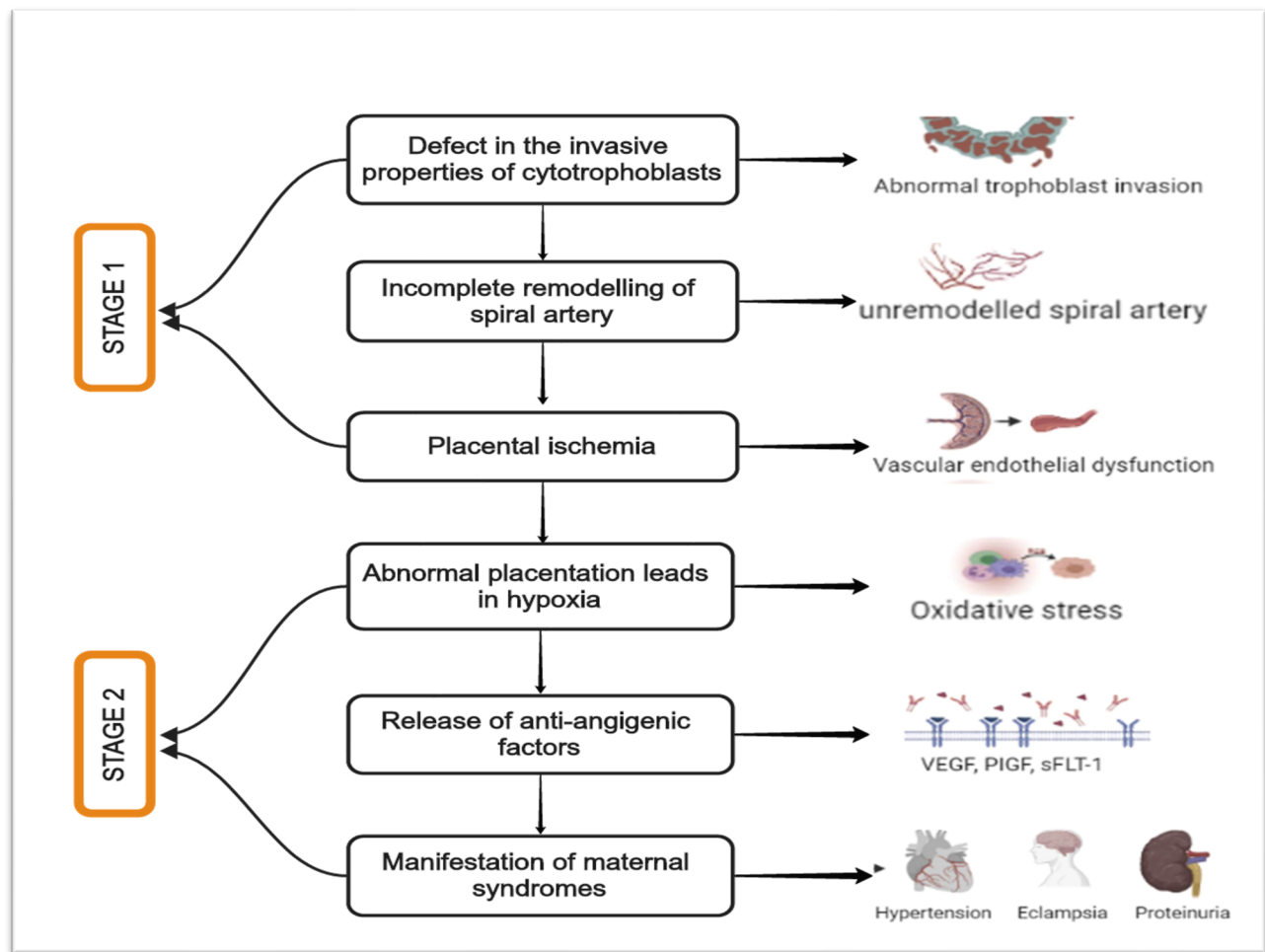
The interpretation of PE epidemiological studies remains complicated because researchers use various definitions to diagnose the condition. Studies have presented multiple diagnostic definitions for PE which have appeared in published literature and professional guidelines. As a result, professional organizations globally have developed multiple protocols for the diagnosis and treatment of PE. ^[1,11,15,16] Nonetheless, an internationally recognized definition of preeclampsia (PE) has been established by the International Society for the Study of Hypertension in Pregnancy (ISSHP) ^[14], as endorsed by the International Federation of Gynecology and Obstetrics (FIGO).

PATHOGENESIS OF PRE-ECLAMPSIA:

The underlying causes of preeclampsia remain unclear although a two-stage process stands as the most commonly accepted origin of this condition.

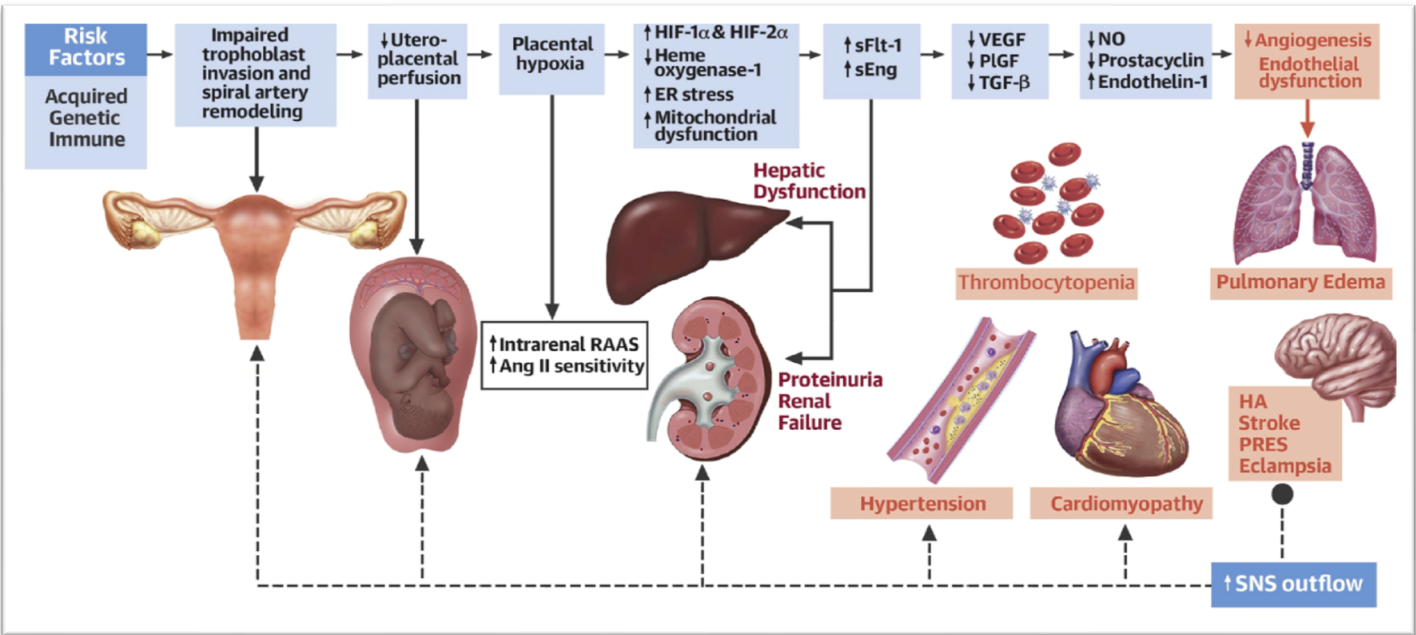
The initial trophoblastic invasion remains limited thereby causing poor spiral artery remodeling. This early stage transitionally leads into a second phase which shows maternal responses to endovascular malfunction alongside an imbalance between pro-angiogenic and anti-angiogenic components that produce distressing clinical symptoms. ^[17-19] The placenta produces antiangiogenic factors like Soluble fms-like

tyrosine kinase-1 (sFLT-1) and Soluble endoglin (sENG) that enter the maternal bloodstream. Elevated sFLT-1 concentrations in PE women lead to proteinuria and damage their kidneys and hypertension but sENG triggers intrauterine growth restriction (IUGR) alongside reduced platelet counts and cerebral edema. The gene expression of sFLT-1 requires reactive oxygen species (ROS) to block VEGF and PlGF functions. This impairs endothelial cell function and causes the organ dysfunction.^[16]



(Figure - 1) Two-phase pathophysiology of PE. Stage 1 features improper placental development and abnormal blood flow patterns. The hypoxic placenta of Stage 2 generates anti-angiogenic agents that enter maternal blood circulation leading to PE.(Sandra Kannampuzha et al. 2022)

Precise prediction together with uniform prevention of PE remains an ongoing major challenge. The early prediction of PE seeks to identify maternal risks leading to PE development among pregnant women. The early detection of conditions allows essential preventive measures to improve placental development thereby minimizing PE occurrence. Additionally, the identification of a "high-risk" category allows for the individualization of antenatal surveillance to predict, identify, and treat the development of the clinical syndrome in a timely manner.



(Figure - 2) Pathogenesis Of Pre-Eclampsia (Aishwarya Gupta et al. 2024)

MATERNAL AND PERINATAL MORBIDITY AND MORTALITY ASSOCIATED WITH PRE-ECLAMPSIA

MATERNAL MORBIDITY AND MORTALITY:

Intracranial hemorrhage stands as the leading cause that results in fatalities among women suffering from pre-eclampsia. Pre-eclampsia can lead to several serious complications including HELLP syndrome along with acute pulmonary edema, placental abruption and acute renal failure and respiratory distress syndrome. ^[21] Chesley et al.^[22] Their research introduced the idea that pregnancy serves as a stress test while studying how women with no pre-eclampsia history show lower cardiovascular risk than other females do. A comprehensive analysis of 24 clinical studies reveals pre-eclampsia history increases women's relative cardiovascular disease risk to 3.13 (95% CI: 2.51–3.89) while their odds of chronic hypertension development reach 2.28 (95% CI: 1.87–2.78) and they exhibit an elevated cardiovascular event probability of 1.8 (95% CI: 1.43–2.21). ^[23] According to a prospective cohort study high subsequent risk of end-stage renal disease developed in patients with PE (Relative Risk of 4.7; 95% CI, 3.6–6.1).^[24] People who experienced pre-eclampsia need awareness about developing cardiovascular disease ^[26-28] and metabolic syndrome ^[25] together with end-stage or chronic renal disease.^[29] Monitoring symptoms of metabolic syndromes combined with appropriate lifestyle changes postpartum for women with PE lowers the associated risks.

PERINATAL MORBIDITY AND MORTALITY:

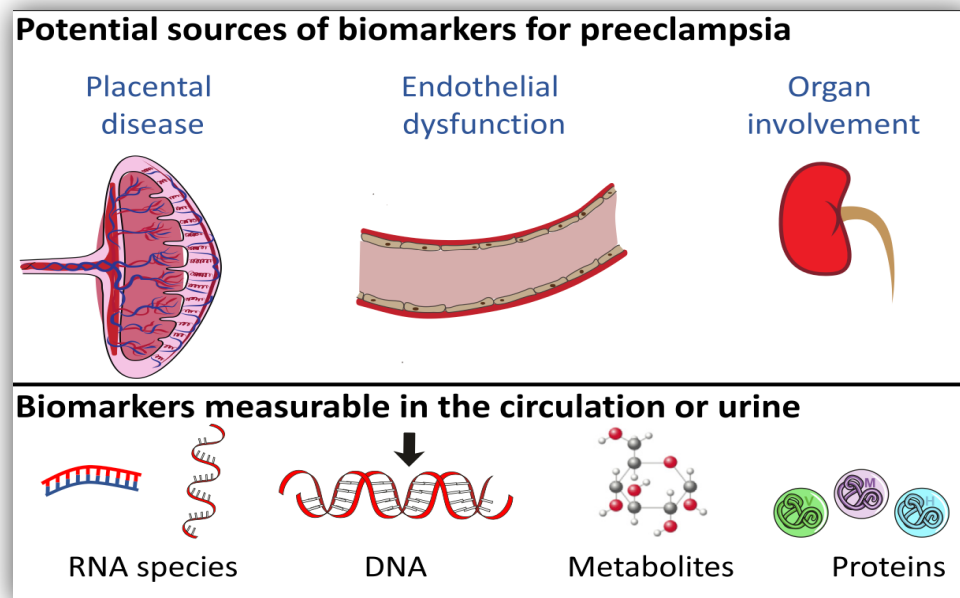
(Table 1) - The following table summarizes perinatal and neonatal complications of pre-eclampsia which have short and long term. ^[30]

SHORT TERM COMPLICATIONS	LONG TERM COMPLICATIONS
• Intrauterine fetal death (IUFD) • Fetal growth restriction • Oligohydramnios • Nonreassuring NST/FHR • Low Apgar score • Need for NICU admission	• Cerebral palsy • Low Intelligence quotient • Hearing, Visual impairment • Diabetes mellitus • Coronary artery disease • Hypertension

The most critical issue with pre-eclampsia demands immediate proper prediction and prevention methods because IUFD remains the main concern. The chance for IUFD varies extensively based on population demographics while also considering PE severity levels and preexisting medical conditions.^[31] Infant mortality rates are three times higher for women with pre-eclampsia across low and middle-income nations in comparison to high-income nations.^[32] Regarding the impact on adult life, the Osmond and Barker et. al ^[33] study supports the notion that conditions from intrauterine life impact both adult health along with disease development. Suboptimal in-utero nutrition caused by placental insufficiency activates metabolic and hormonal adaptations along with organ morphological alterations that increase the potential for insulin resistance and diabetes mellitus alongside coronary artery disease and hypertension.

PREDICTION OF PRE-ECLAMPSIA USING CLINICAL TOOLS AND BIOMARKERS:

The need for predictive biomarkers for preeclampsia has been consistently rising. A suitable predictive test enables rapid detection for individualized monitoring followed by early treatment. A biomarker which identifies high-risk pregnant women prior to 16 weeks of pregnancy provides clinical value to prevent preterm preeclampsia and preterm birth as well as perinatal morbidity by enabling low-dose aspirin prophylaxis treatment for premature disease prevention. The identification of individuals at increased risk for preeclampsia in late stage of pregnancy, which allows for increased prenatal surveillance and timely delivery, has been proven by the findings of the PHOENIX trial by Prof. Lucy C. Chappell et al. in 2019. [34]



(Figure -3) Sources and types of biomarkers that could be analyzed for preeclampsia assessment. (Teresa M MacDonald et al.2021)

Blood pressure monitoring functions as a preeclampsia screening method that medical professionals have used since the early 1900s. The diagnostic value of high blood pressure becomes apparent after preeclampsia commences but fails to effectively predict future occurrences of the condition. Early pregnancy testing for preeclampsia includes detecting clinical risk factors yet exhibits minimal predictive potential (*Table 2*).

Two screening tests were introduced for clinical practice during the past decade throughout various clinical settings. These 2 screening approaches exist with different targets: First-trimester screening identifies high-risk patients for preterm pre-eclampsia development while the second test assesses late pregnancy women who face uncertainties about preeclampsia risk. The latter test demonstrates a high negative predictive value for PE development while simultaneously displaying exceptional accuracy at determining preeclampsia risk (positive prediction value).

⇒ **CLINICAL GUIDELINES FOR THE APPLICATION OF A PRE-ECLAMPSIA RISK SCORE:**

According to ACOG and NICE guidelines previous preeclampsia together with chronic renal disease and chronic hypertension and preexisting diabetes mellitus and autoimmune disease constitute the highest risk factors for PE. The ACOG guidelines include multifetal gestation as one of its risk factors which NICE classifies as moderate. The combination of ≥ 2 mild risk criteria classifies women as pre-eclampsia high-risk cases. Among these moderate risks factors are nulliparity and advanced age with high BMI values as well as ≥ 10 -year inter pregnancy intervals

and familial preeclampsia history. These protocols provide effective guidelines for treating all pregnant patients without any extra diagnostic methods or financial expenses but demonstrate inadequate detection abilities. ^[35,36]

⇒ **FIRST TRIMESTER COMBINED ALGORITHM:**

A new validated screening algorithm uses first-trimester assessment to predict preterm preeclampsia as a solution to the deficiency seen in clinical risk factor score. The screening protocol combines mean arterial blood pressure measurements with Doppler ultrasound examination of uterine artery resistance index alongside circulating placental growth factor (PlGF). Compared to clinical risk factor evaluation alone this screening test displays enhanced effectiveness in anticipating preterm preeclampsia occurrence. ^[35,36]

CURRENT TESTS USED FOR EVALUATION OF PRE-ECLAMPSIA ^[37]

(Table -2)

<u>TEST</u>	<u>SPECIFICATIONS</u>	<u>ADVANTAGES</u>	<u>DISADVANTAGES</u>
Clinical guidelines for PE risk score application. Given by National Institute for Health and Care Excellence and American College of Obstetricians and Gynecologists.	The combination of maternal characteristics along with pregnancy conditions and co-existing medical problems classifies as either high risk or moderate risk factors.	1) It necessitates an evaluation of easily accessible clinical factors. 2) The assessment applies to every pregnant woman during her first ANC visit so healthcare professionals can determine which patients require low-dose aspirin medication for preterm preeclampsia prevention. 3) This method requires no specific blood tests or Doppler ultrasonography. 4) No additional cost required.	1) Limited test performance. The diagnostic tool shows a sensitivity of 41% specifically for pre-term pre-eclampsia and demonstrates reduced accuracy across all pre-eclampsia cases. 2) The practical observations demonstrate that women at risk do not show consistent adherence to low-dose aspirin as a preventative measure.

First trimester screening with combined algorithm for evaluation of preeclampsia	Risk assessment evaluates maternal characteristics while incorporating both mean arterial blood pressure and mean uterine artery resistance index measurements with circulating PlGF measurements.	1) Achieves a sensitivity exceeding 82% for preterm preeclampsia. 2) Proven to attain a high level of compliance with prophylactic aspirin.	1) The testing process of PlGF from blood samples together with ultrasonography of maternal uterine arteries resistance requires extra expense. 2) This method does not demonstrate high sensitivity in predicting term pre eclampsia. Identifies only 42.5% of all cases of preeclampsia. 3) The combination of its use with aspirin prophylaxis does not decrease the incidence of preeclampsia occurring after 37 weeks, which constitutes the majority of cases.
--	---	---	---

Soluble fms-like tyrosine kinase 1 (sFlt-1) : Placental growth factor (PIGF) Ratio	Value exceeding than 38 indicates screening positive	1) sFlt1:PIGF measurement at or below 38 points demonstrates a 99.3% probability that pre-eclampsia will not develop within the following week therefore making it a reliable test to eliminate pre-eclampsia as a diagnosis. ("rule-out" test). 2) This methodology helps prevent hospital admissions of women who are suspected of having pre-eclampsia.	1) Applicable only to suspected pre-eclampsia at beyond 37 weeks; and not relevant to the general pregnant women. 2) Assessment of pre-eclampsia development remain imprecise with poor sensitivity and positive predictive value performance rates.
Placental growth factor (PIGF)	Value of <100pg/ml indicates screening positive	1) The diagnostic accuracy of this test for identifying preeclampsia risk among pregnant women below 35 weeks period of gestation stands at sensitivity of 96% and negative predictive value of 98% when monitoring	1) This screening method targets individuals who are suspected of having preeclampsia before week 35 of pregnancy but does not assess the normal pregnant population.

		developing preeclampsia over the following 2 weeks. 2) The implementation of this test has demonstrated decreased diagnostic timelines while reducing unfavorable maternal health consequences along with outpatient doctor appointments and healthcare expenses.	2) Can not predict which individuals will develop preeclampsia at term.
--	--	---	--

A study by Leona C.Y. Poon, Nikos A. Kametas, Nerea Maiz et al. (2009) ^[38] showed that PlGF screening along with pregnancy-associated plasma protein A (PAPP-A) and uterine artery Doppler tests in the first trimester can detect early-onset PE effectively while maintaining a 5% false-positive rate in low-risk women. Screening early onset PE among healthy people becomes a realistic option because five percent of potentially positive test results would result in later PE diagnosis.

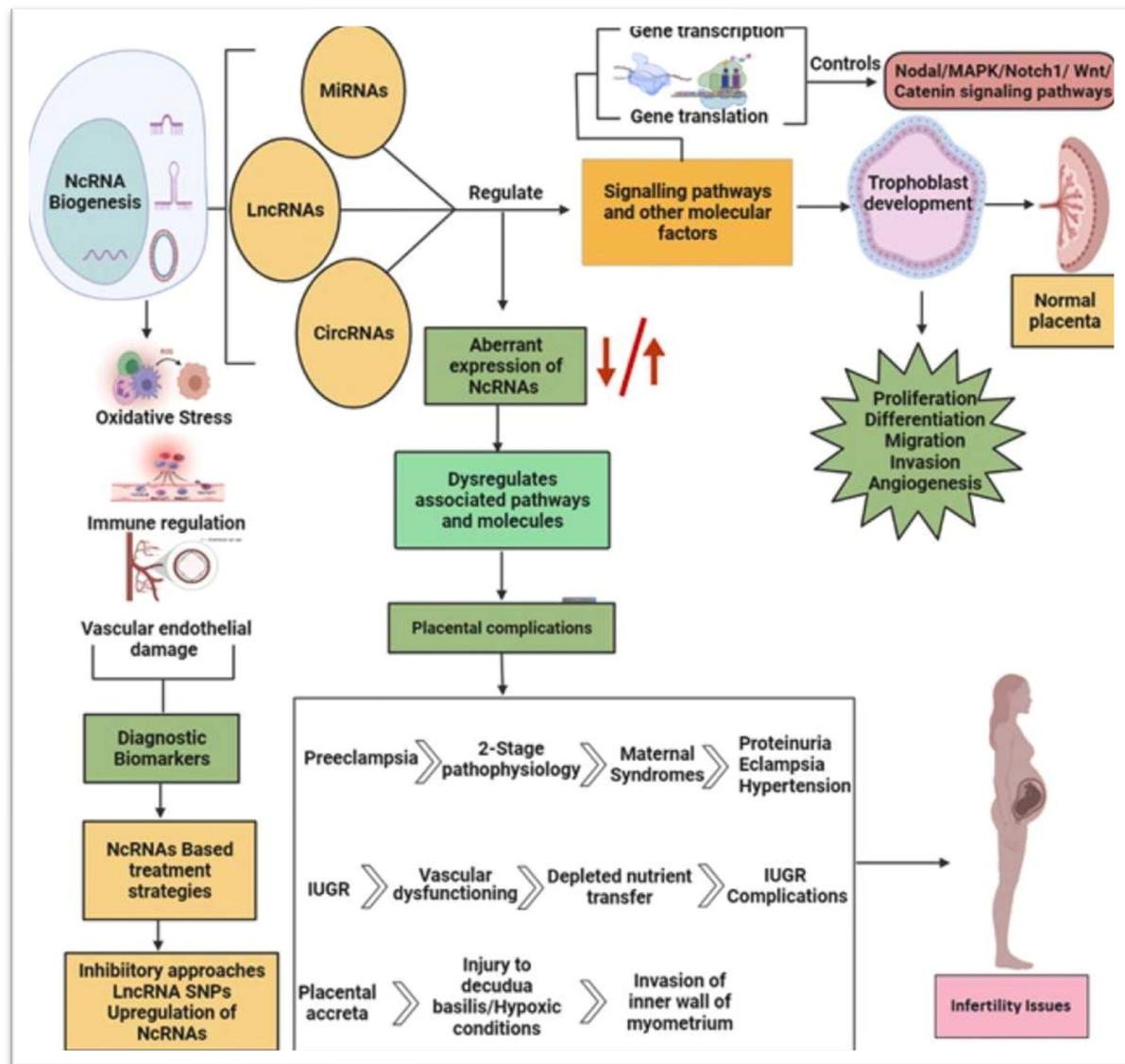
A study by Lagana AS, Domenico Giordano et al. (2017) ^[39] demonstrated that first-trimester pregnancy peripheral blood tests of circulating endothelial progenitor cells together with natural killer cells can predict the risk of pre-eclampsia development.

The combination of biochemical and molecular biomarkers forms a plausible screening and diagnostic tool for the detection of PE. The placenta-originated stable noninvasive molecular markers that circulate in maternal plasma or serum include miRNAs. Multiple studies reveal that preeclampsia causes specific miRNA expression changes to occur in placentas and maternal serum (Lagana` and Vitale SG et al. 2018). ^[40]

NON-CODING RNAs:

A recent high-throughput transcriptome studies show that ~90% of eukaryotic genomic DNA is transcribed. The majority of these transcripts are translated into non-coding RNAs (ncRNAs) while about 1% to 2% encode different proteins. The regulatory influence of ncRNAs shows evidence in developmental processes as well as stress-related and environmental response pathways. The identification and functional characterization of the entire spectrum of noncoding RNAs (ncRNAs) in relation to normal physiological functions and their roles in medical conditions is a primary objective of conventional molecular biology. ^[41,42]

Non-coding RNAs function as two main categories which include infrastructure-related and regulatory functions. The class of constitutive ncRNAs contains Ribosomal RNAs, Transfer RNAs, Small Nuclear RNAs and Small Nucleolar RNAs. MicroRNAs (miRNAs) belong to a regulatory ncRNA group together with Piwi-interacting RNAs (piRNAs) and small interfering RNAs (siRNAs) as well as long non-coding RNAs (lncRNAs). Recently, Enhancer RNAs (eRNAs) emerged as a novel promoter-associated RNA (PAR) subclass. ^[43]



(Figure- 4) Mechanism of ncRNAs in PE (Sandra Kannampuzha et al. 2022)

(Table-3) TYPES OF NCRNAS AND THEIR BIOLOGICAL ROLES ^[44]

TYPE	LONG NAME	LENGTH (NT)	CHARACTERISTICS	FUNCTION
miRNA	Micro RNA	20 to 24	1) The nucleus produces pri-miRNA as polyadenylated and capped single stranded RNA with stem-loop structure that has improper base pairing. 2) Drosha and Dicer's processing results in the generation mature dsRNA with structured terminal ends. 3) The Ago protein regulates the effector phase, which mostly takes place in the cytoplasm.	1) Complete complementarity: Ago2-mediated mRNA cleavage 2) mRNA breakdown (deadenylation, decapping, and exonucleolytic degradation) or translation suppression are examples of non-perfect complementarity. 3) Insignificant roles for translational activation and transcriptional silencing
piRNA	PIWI-interacting RNA	24 to 31	1) The modified precursor ssRNA includes 3-terminal 2-O-methyl 2) The 5 end Uridine is highly preferred.	Transposable germline genes remain in a state of dormancy.
siRNA	Small interfering RNA	20 to 24	1) Long, linear base-paired dsRNA in canonical form 2) Dicer transforms it into mature siRNA with a diverse final composition.	1) Endonucleocytic cleavage is the ideal match. 2) Endonuclease-inactive RISC or non-perfect match: exonucleolytic degradation or translational suppression

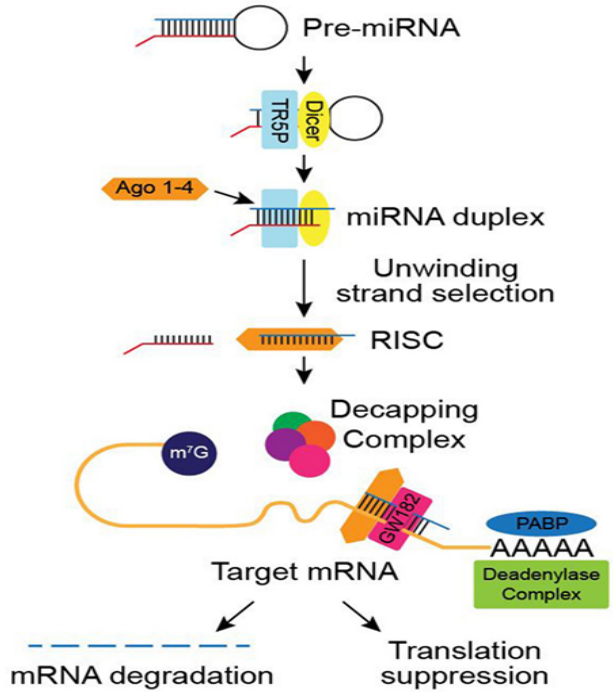
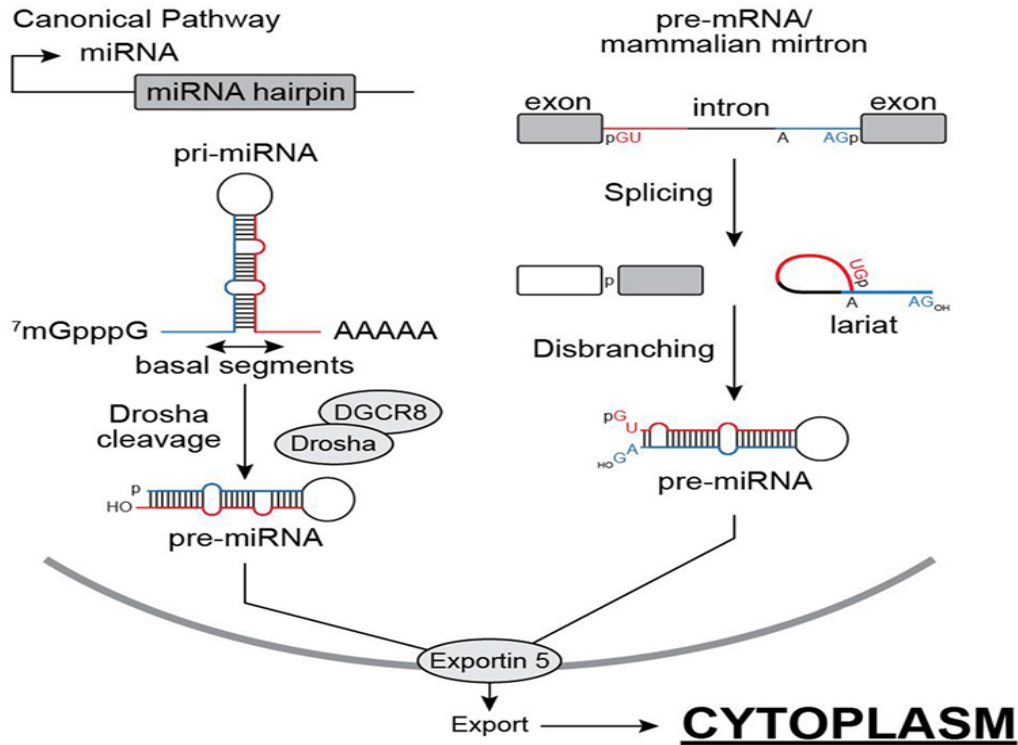
			3) Ago proteins promote effector actions, which mostly take place in the cytoplasm.	3) Induction of development of heterochromatin. 4) The locus becomes inactive from where the initial genetic material originated.
PAR (PASR, TSSa-RNA, tiRNA, PROMPT)	Promoter-associated RNA	16 to 200	1) ssRNAs which are expressed weakly. 2) Shorter half-life 3) A bidirectional expression that reflects the spread of Pol II	Signs of transcriptional regulation that are partially unknown (e.g., association with the Polycomb class of proteins)
eRNA	Enhancer RNA	100 to 9000	1) The ssRNA molecular sequences derived from enhancer elements demonstrate two-directional RNA synthesis while containing Pol II protein and H3K4me1 modifications alongside coactivator p300. 2) Limited half-life. 3) Sequences that are preserved across evolution 4) Adaptively controlled by signaling. 5) The degree of expression demonstrates a positive relationship with the transcriptional activity of proximal mRNA.	Mostly undiscovered but involved in the activation of transcriptional genes

lncRNA	Long non-coding RNA	>200	1) The precursor single stranded RNA 2) Variety of post-transcriptional changes, including splicing and polyadenylation, can affect lncRNAs. 3) The majority of RNAs originate from the cell nucleus yet the cytoplasm contains a tiny fraction of these molecules. 4) Except for lincRNAs (H3K4me3-H3K36me3 signature) and large intergenic ncRNAs, they are not evolutionary conserved.	1) Remodeling of chromatin Regulation of transcription 2) Post-transcriptional modulation (Transcription Factors localization, splicing) 3) SiRNA precursors 4) A constituent of nuclear organelles, such as nuclear and paraspeckles
---------------	---------------------	------	---	---

The complexity and heterogeneity of pre-eclampsia complicate its diagnosis, prediction, and therapy. Due to the inability to identify the molecular patterns of the primary afflicted organ, the placenta, until pregnancy terminates, prompt monitoring of PE progression is challenging. Consequently, biomarkers present in peripheral blood have significant potential for noninvasive surveillance. Various biochemical indicators can identify placental growth factor together with soluble FMS-like tyrosine kinase receptor 1 and PP13 (placental protein 13) as well as placental protein A within serum though their diagnostic value (sensitivity and specificity remains low) remains limited. Screening and diagnosing pre-eclampsia demonstrate better precision through molecular biomarkers than biochemical indicators. Maternal peripheral blood-derived ncRNAs are anticipated to serve as potential noninvasive biomarkers. A wide array of research investigations focused on ncRNAs found in peripheral blood samples from PE patients. ^[45]

miRNAs (MicroRNAs) AND PRE-ECLAMPSIA:

NUCLEUS



(Figure- 5) illustrates the conventional pathway of miRNA biogenesis where RNA polymerase II initiates transcription of pri-miRNA molecules within the nucleus. These primary sequences then undergo processing by the Drosha–DGCR8 complex to generate pre-miRNAs. The transport of precursor miRNAs through Exportin 5 enables their entry into the cytoplasm for Dicer-TRBP processing that finally results in their integration into AGO2-RISCs which inhibits target gene expression. The binding of GW182 to PABP blocks mRNA circularization during a process that leads to accelerated RNA breakdown. Additionally, miRNAs can be produced through non-canonical pathways which do not require Drosha cleavage. (Kelsey R. Bounds et al. 2017)

Small noncoding RNA molecules known as miRNAs consist of 20-24 nucleotides that control gene expression through targeting of seed sequences located in 3'-untranslated regions (UTRs) of mRNAs which eventually results in translation reduction and fragmented mRNA. The biological process of gene expression functions through miRNAs as they target messenger RNAs (mRNAs) to cause translation repression while degrading RNA molecules. ^[46].

Genome sequences containing their own promoter regions generate naturally occurring small non-coding RNAs known as miRNAs within cells. The transcription products from miRNAs produce stem-loop structures that measure an average of 70 nucleotides in length. These molecules achieve gene regulation by attaching to target gene mRNAs to cause post-transcriptional repression. ^[47,48]

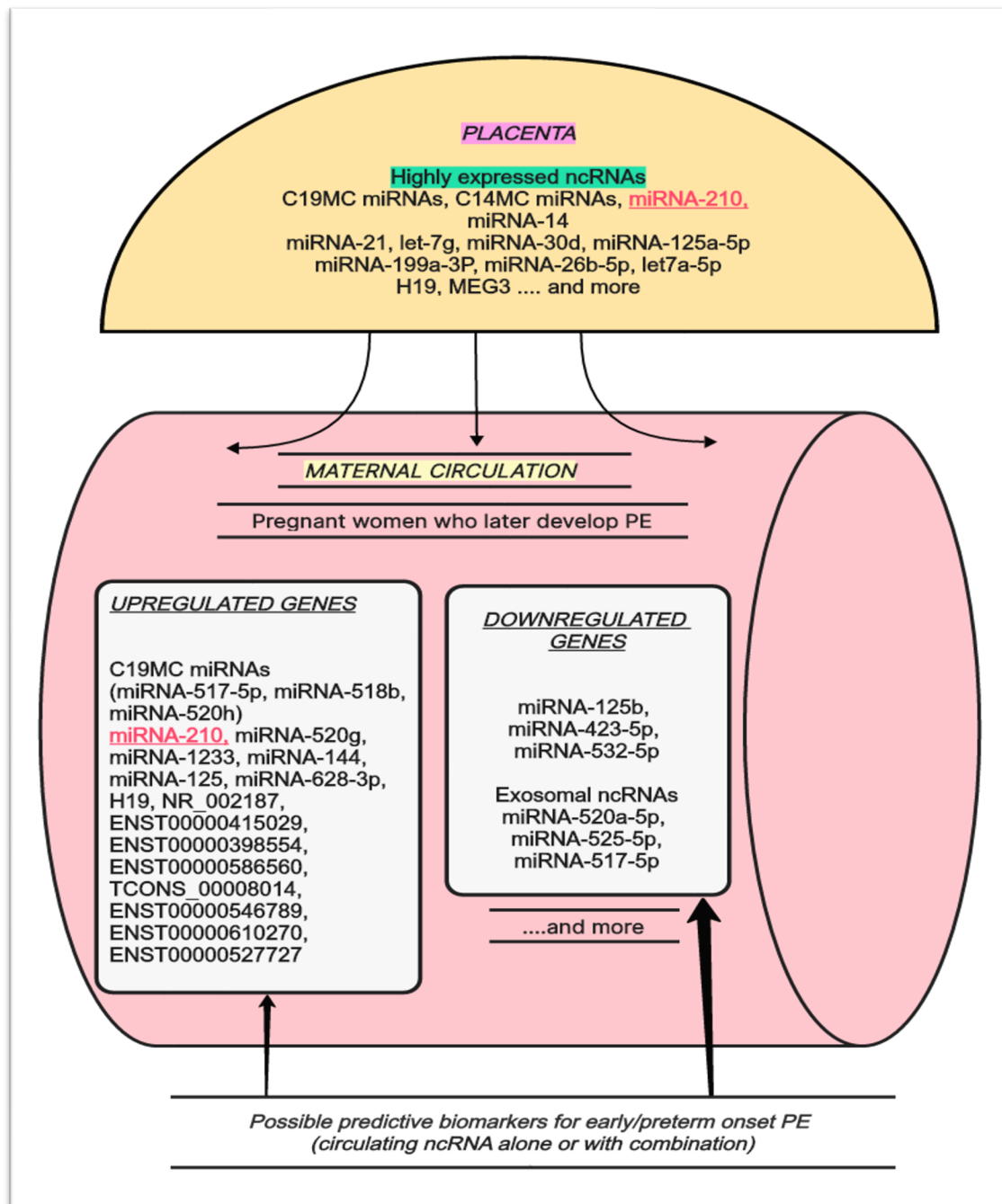
Some miRNAs possess unique binding ability to target mRNAs that results in their destruction process. A failure of miRNAs to properly align with target mRNA 3'UTR regions leads to translation process disruption. The nuclear channel initiates

precursor miRNA transcript processing through Drosha and RNase III while the karyopherin-exportin 5 complex facilitates their nuclear export. The exonuclease activity of Dicer transforms precursor miRNAs into 21-22 nucleotide microRNAs within the cytoplasmic compartment. [49]

Next, the miRNA duplex binds to the RNA induced silencing complex (RISC) for processing within the argonaute (AGO) family in conjunction with two cofactors: protein kinase RNA (PACT) and protein activator of interferon induced protein kinase (PRKRA). The target mRNA identification of RISC by miRNAs leads to two potential outcomes: mRNA cleavage or translational suppression. miRNAs belong to a class of small non-coding RNA molecules that bind mRNA targets to activate post-transcriptional repression. The regulation of gene expression depends fundamentally on the action of miRNAs. Single miRNA expression variation creates a chain reaction throughout multiple cell genes which leads to simultaneous changes in their translation capabilities causing altered cell phenotypic expression.

The modifications of miRNAs can potentially modify their target affinity or functioning ability. miRNA editing enhances multiple stages of miRNA production thereby modifying target mRNAs while providing regulatory control to the RNA-mediated gene functional network. RNA editing proteins ADARs control miRNA biogenesis through their role as adenosine deaminases acting on RNA.

Several studies reveal that disturbances in miRNA homeostasis indicate the presence of pathological conditions inside the body. The abnormal expression of miRNAs causes changes in cell processes such as proliferation and differentiation and apoptosis which links miRNA modifications to pathological conditions. [50,51]



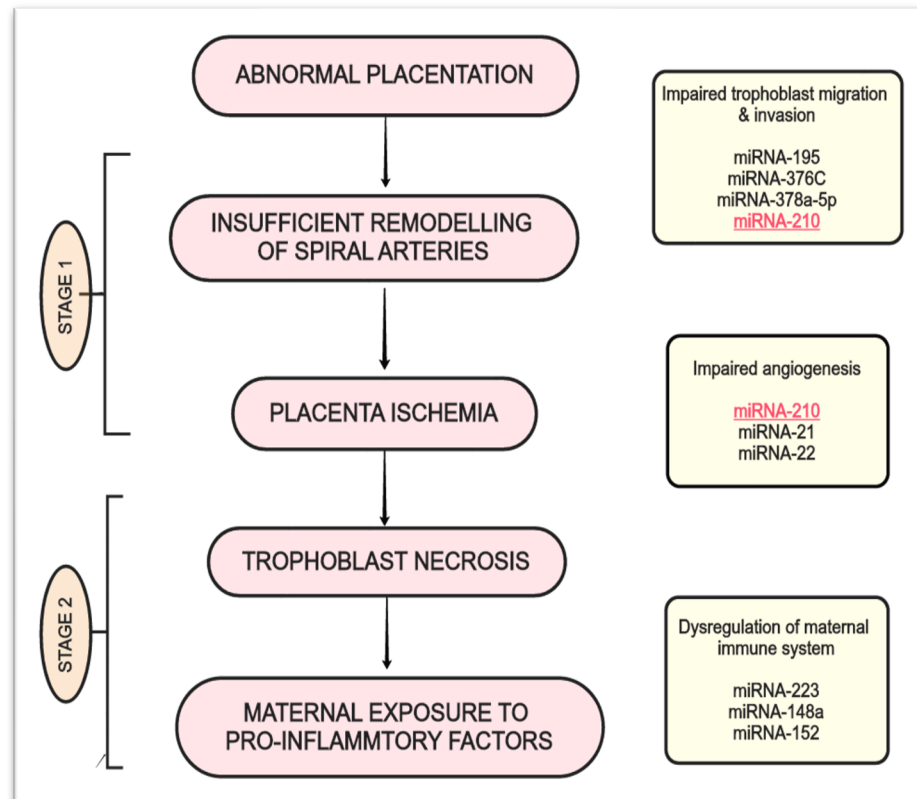
(Figure-6) presents potential biomarkers used for predicting both early and preterm cases of PE. High levels of ncRNAs produced by the placenta together with extravillous trophoblasts are responsible for early placentation and contribute to both early/preterm onset PE development.(Manabu Ogoyama et al. 2022)

(Table-4) SEVERAL miRNAs INVOLVED IN PRE-ECLAMPSIA^[52]

SOURCE	REGULATION	miRNAs	METHOD OF DETECTION	REFERENCES
Placenta	Upregulated	miRNA-210	Microarray and (Quantitative Reverse Transcription Polymerase Chain Reaction) qRT-PCR	Enquobahrie et al. (2011)
		miRNA-515-3p, miRNA-31, miRNA-210, miRNA-518a, miRNA-524, miRNA-518c, miRNA-520a, miRNA-515-5p, miRNA- 516a-5p, miRNA-519e, miRNA-193b, miRNA-4532, miRNA-518f, miRNA-527, miRNA-518e	Next Generation Sequencing (NGS)	Vashukova et al. (2016)
		miR-30a-3p	qRT-PCR	Niu et al. (2018)
Placenta	Downregulated	miRNA-1247, miRNA-328, miRNA-584, miRNA-139-5p, miRNA-500, miRNA-34c- 5p, miRNA-1	Microarray and qRT-PCR	Enquobahrie et al. (2011)
		miRNA-135b, miRNA-195, let-7f, miRNA- 34c, miRNA-1, miRNA-98, miRNA-223	NGS	Vashukova et al. (2016)

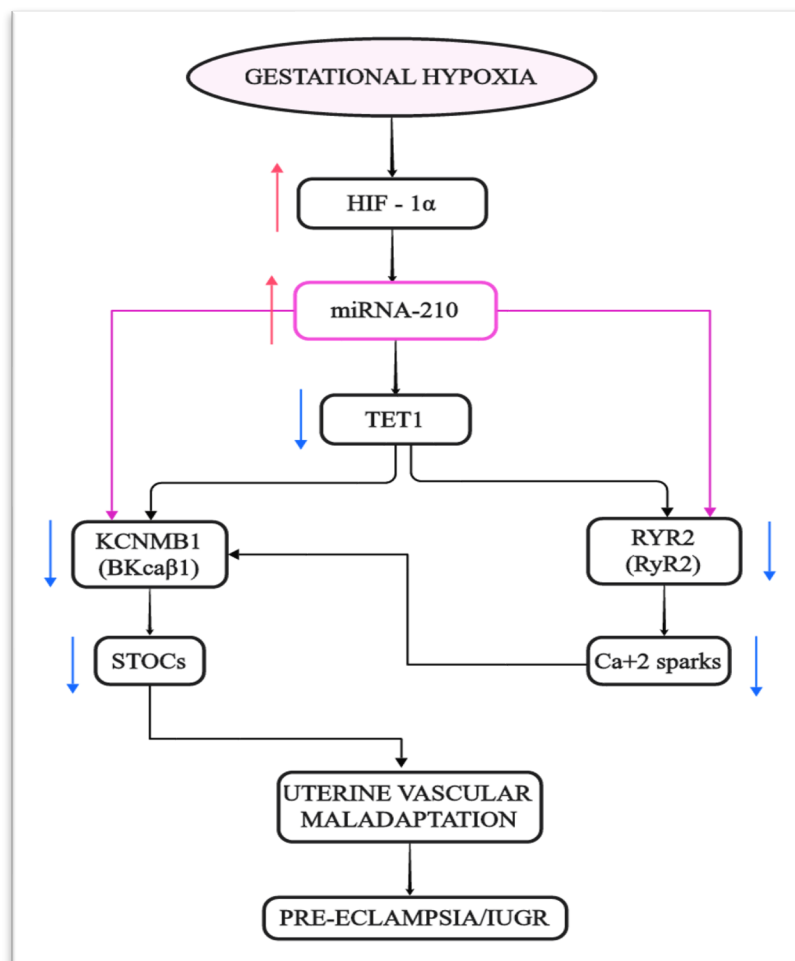
		miRNA-532-5p, miRNA-423-5p, miRNA-127-3p, miRNA-539-5p, miRNA-519a-3p, miRNA-629-5p, let-7c-5p	NGS and qRT-PCR	Timofeeva et al. (2018)
Maternal plasma	Upregulated	miRNA-141, miRNA-29a	NGS and qRT-PCR	Li et al. (2013)
		miRNA-24, miRNA-26a, miRNA-103, miRNA-130b, miRNA-181a, miRNA-342-3p, miRNA-574-5p	Microarray and qRT-PCR	Wu et al. (2012)
		miRNA-215, miRNA-155, miRNA-650, miRNA-210, miRNA-21	qRT-PCR	Jairajpuri et al. (2017)
		miRNA-423-5p, miRNA-519a-3p, miRNA-629-5p, let-7c-5p	NGS and qRT-PCR	Timofeeva et al. (2018)
Maternal plasma	Downregulated	miRNA-144	NGS and qRT-PCR	Li et al. (2013)
		miRNA-18a, miRNA-19b1	qRT-PCR	Jairajpuri et al. (2017)
Maternal serum	Upregulated	miRNA-210, miRNA-520a, miRNA-1233	Microarray and qRT-PCR	Ura et al. (2014)
		miRNA-152, miRNA-183, miRNA-210, miRNA-182	qRT-PCR	Li et al. (2015)
	Downregulated	miRNA-144	Microarray and qRT-PCR	Ura et al. (2014)

(Figure 7) – Various miRNAs involved in pathogenesis (Stage 1 & 2) of PE
(Georgios Skalis et al. 2019)



THE ROLE OF miRNA-210 IN PRE-ECLAMPSIA:

The circulating miRNA-210 originates from the placenta and plays an essential role in hypoxia-triggered disturbances which cause trophoblast vascular endothelial impairment during pre-eclampsia. The miRNA-210 shows elevated expression in preeclampsia-affected placentas according to multiple independent scientific studies. ^[53,54]

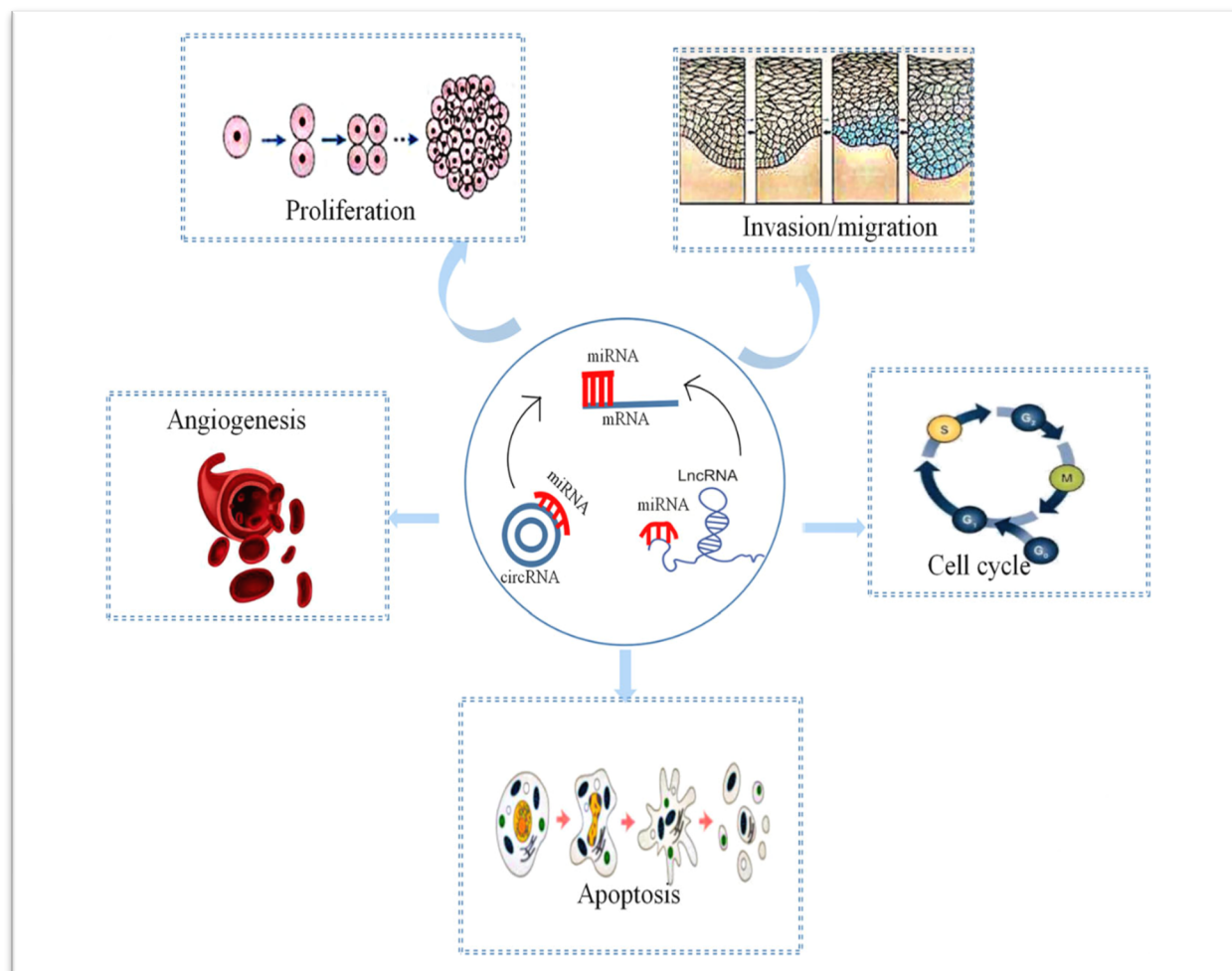


(Figure -8) - During gestation miRNA-210 under hypoxic conditions repress spontaneous transient outward currents in uterine arteries (Xiang-Qun Hu et al. 2021)

The initial analysis conducted by Pineles et al. (2007) ^[55] utilized qRT-PCR to investigate 157 miRNAs which demonstrated increased miRNA-210 levels in preeclampsia-affected placentas. The research findings from Zhu et al., together with subsequent work of Mayor-Lynn et al. and Enquobahrie et al. reported elevated miRNA-210 expression levels are seen in pre-eclamptic women. ^[56,57] The genomic locus of transcript AK123483 contains miRNA-210 as an intronic miRNA. The

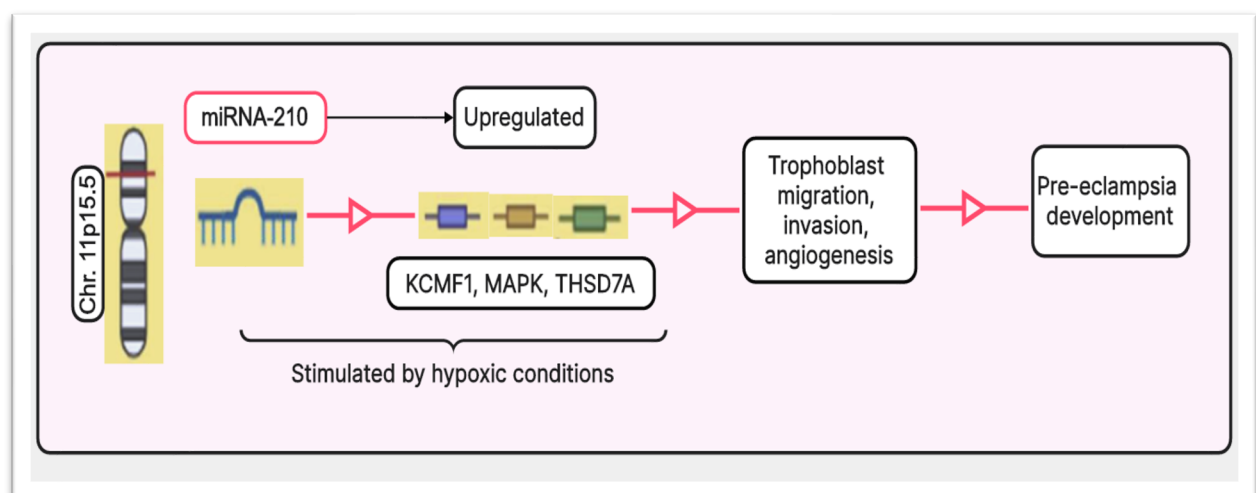
expression of miR-210 depends on regulatory factors such as hypoxia-inducible factors (HIF-1 α , HIF-2 α) together with NF- κ B.^[58]

Placental miRNA-210 shows higher expression levels in cases of preeclampsia yet its identified targets remain limited for understanding preeclampsia pathogenesis. Abnormal expression of miRNA-210 correlates directly to hypoxic conditions which restrict both trophoblast invasion capabilities and spiral artery remodelling therefore triggering preeclampsia onset.^[59] HIF-1 α protein mediates this process by binding to the HIF-responsive element situated 400 base pairs above the proximal promoter.



(Figure - 9) demonstrates how ceRNAs composed of lncRNAs and circRNAs guide microRNA targets to achieve competitive endogenous RNA control over Trophoblast cell proliferation and invasion, migration and apoptosis throughout the G0/G1 phase. (Ningxia Sun et al. 2021)

The overexpression of miRNA-210 allows hypoxia-inducible factors (HIFs) to modulate hypoxic cellular responses through gene regulation of erythropoiesis along with differentiation, inflammation, angiogenesis, cell proliferation, apoptosis and metabolism.^[60]



(Figure - 10) The overexpression of miR-210 disrupts different biological processes starting from placental angiogenesis to trophoblast cell invasion and migration events. (Sandra Kannampuzha et al. 2022)

The research done by Zhang et al. (2012) discovered increased miRNA-210 expression in preeclampsia placenta samples while showing hypoxic conditions trigger rapid miRNA-210 elevation in trophoblast cell line. This study showed that NF-kB p50 and HIF-1 α both regulate miRNA-210. Homeobox-A9 (HOXA9) and

ephrin-A3 (EFNA3) serve as miRNA-210 direct targets while performing diverse genetic functions that include cellular migration as well as embryonic vascular remodeling and developmental processes. The downstream genes that encode KCMF1, NOTCH1, and MAPK become miRNA-210 targets potentially disrupting trophoblast invasion together with proliferation and angiogenesis.^[61]

According to Luo et al. (2014) ^[62] KCMF1 levels exhibited an opposite relationship with miRNA 210 expression levels and presented reduced amounts in PE patient placental tissue. The dual luciferase method demonstrated experimentally that KCMF1 functions directly as a target of miRNA 210 in HTR8/SVneo cells. Furthermore, tumor necrosis factor- α (TNF- α), an inflammatory factor, suppress KCMF1 levels while increasing miRNA-210 expression. Therefore, by disrupting KCMF1 mediated signaling in the human placenta, aberrant miRNA-210 expression potentially contributes to the development of PE.

According to Murali Manoharan et al. (2012) ^[63] placentas with PE had mitochondrial dysfunction, which was linked to increased reactive oxygen species (ROS) production and stable Hypoxia-inducible factor -1 levels. Additionally, they further discovered that PE placentas had downregulated ISCU (iron-sulfur cluster scaffold homolog) and upregulated miRNA-210. According to their findings, mitochondrial function is suppressed by miRNA-210 upregulation through mitochondria-associated ISCU.

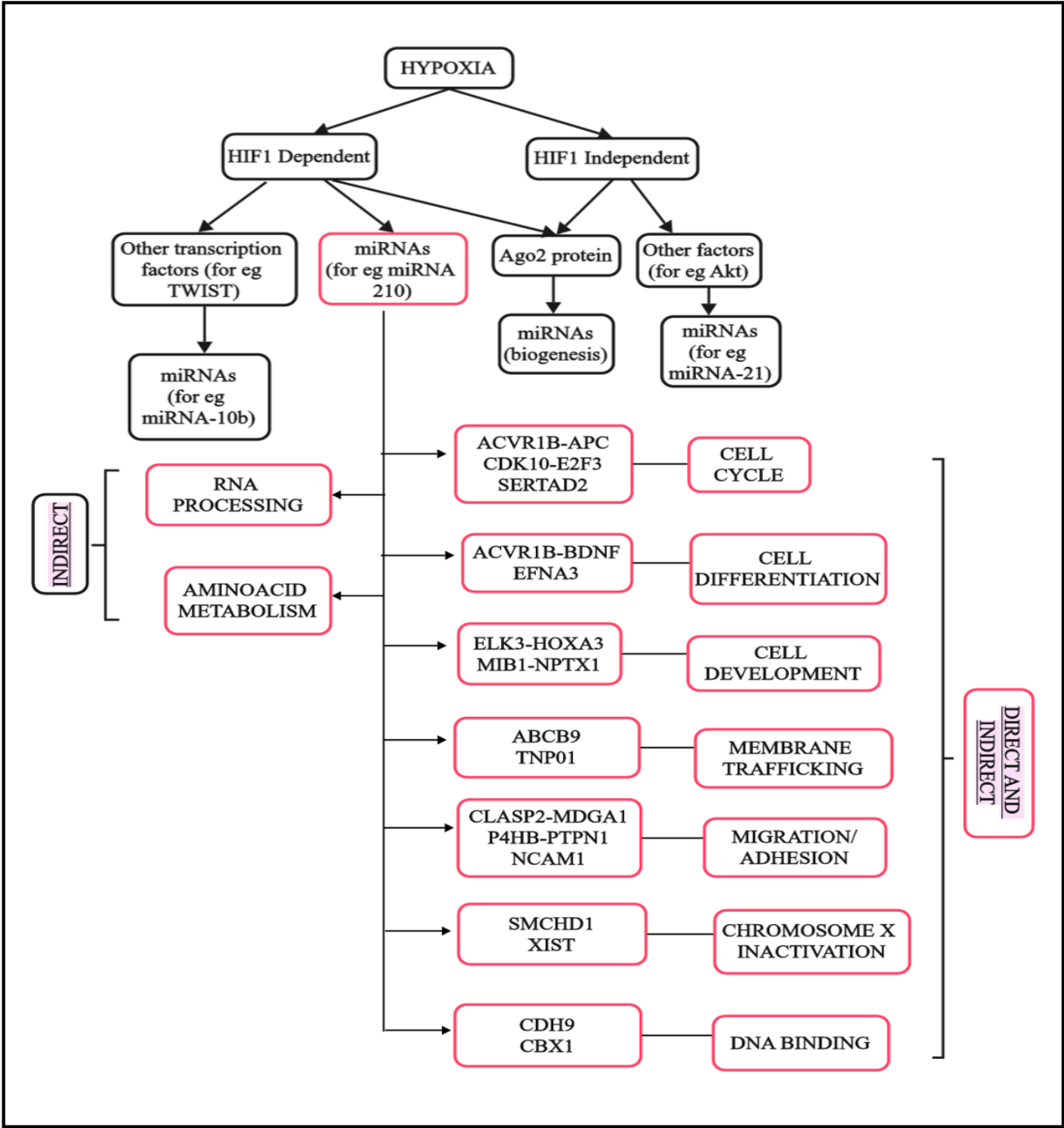
The hypoxia-induced experiment of Lee et al. (2011) ^[64] demonstrated that Swan-71 trophoblasts showed increased iron deposition. They observed elevated retention of intracellular iron and reduced matrigel invasion in Swan-71 trophoblasts when the ISCU was transfected with inhibitors. This implicates that miRNA-210-mediated

ISCU reduction might prevent trophoblast invasion that leads to PE. This study represents a new pathophysiological link between miRNA-210 and PE development.

The specific function of miRNA-210 emerges prominently through its control of cell division together with DNA damage responses and mitochondrial oxidative metabolism and angiogenesis regulation. Due to its biogenesis and physiological significance, miRNA-210 is a prospective gene for use as a prognostic biomarker for therapeutic interventions and future treatment strategies.^[65]

Several studies have found preeclampsia through markers, including plasma microRNAs (miRNAs), which function as gene regulators ^[56]. Despite the association of mRNAs with the pathophysiology of PE, the findings remain ambiguous ^[57, 60]. Research has identified several miRNAs, including miRNA-210 and miRNA-155, in maternal circulation that correlate with an elevated risk of preeclampsia (PE) ^[61]

(Figure - 11) - showing a summary of cellular processes which miRNA-210 modifies through direct and indirect influences based on GO (Gene Ontology) analysis. (Guomin Shen et al. 2013)



The hypoxia-induced miRNA group, or hypoxamiRs, is expressed by miRNA-210 and is present in both normal and altered cells as a response to hypoxia. [61, 85]

Hypoxia has been established as a characteristic of preeclampsia, and miRNA-210 is increased by hypoxia-inducible factor-1 α under hypoxic conditions, identified as the mediator between preeclampsia and miRNA-210 [66]. R Kannan Mutharasan et. al [67] have reported that hypoxic tissue has higher levels of miRNA-210, either in an HIF-dependent or HIF-independent way. Consequently, miRNA-210 may serve as a prospective biomarker for the early identification and diagnosis of preeclampsia [68]. Plasma tests demonstrate that miRNA-210 exists in circulating blood while also revealing its detectable levels in plasma samples. [69]

Recent studies have shown that PE pathophysiology links to specific changes in plasma-associated miRNA levels particularly miRNA-210 and miRNA-155. The serum and urine expression levels of miRNA-210 in preeclamptic women can be examined. Discrepancies were identified when compared to healthy pregnancies in an attempt to evaluate possible biomarkers for predicting the risk of preeclampsia. The analysis of these miRNAs may yield insights into the pathophysiological mechanisms of PE. [70-73]

Despite substantial research by experts on the etiology of preeclampsia, the underlying causes remain unresolved, complicating early detection and risk assessment and impeding effective prevention and treatment efforts. The identification of novel biomarkers linked to preeclampsia may facilitate early diagnosis and aim to uncover the molecular processes that result in this pregnancy related condition, therefore enabling targeted therapeutics and preventive strategies. [74]

Therefore, it is imperative to conduct research for identification and validation of new preeclampsia biomarkers to improve pregnancy outcomes across the globally.

Also, existing invasive methods, including amniocentesis and chorionic villus sampling, result in miscarriage. Thus, development of non-invasive methods are developed for diagnostic and prognostic purposes because of these limitations. miRNA analysis through circulating fluids is possible because these molecules exist steadily in multiple bodily liquids.

The analysis of biomarkers at the molecular level within peripheral blood along with saliva and urine offers a non-invasive approach. Biomarker testing provides a combination of accuracy and affordability for early screening, prognosis assessment, along with disease monitoring in pre-eclampsia. Early pre-eclampsia diagnosis occur through screening for women who are at elevated risk to start prompt interventions aimed at preventing preeclampsia complications. Additional research must be done to properly validate and maximize the effectiveness of biomarkers for better objective diagnosis and prediction outcomes. ^[75]

The main purpose of this study is to establish circulating miRNA-210 as a non-invasive molecular prognostic marker to predict pre-eclampsia onset in women with elevated risk factors. The incidence, progression, and diagnosis of PE continue to pose for challenge in clinical research. Nevertheless, current diagnosis predominantly depends on blood pressure assessments, hematological evaluations, and urine examination (proteinuria).

I Did a Literature Search about same topic.

Robert Morey, Lara Poling, Srimeenakshi Srinivasan et al. (2023) ^[76]; study done at California, San Diego, La Jolla, CA, USA on total of 131 women. This case - control study aimed to detect ex-miRNA indicators for diagnosing pre-eclampsia while predicting its prognosis among women under evaluation for pre-eclampsia. Small RNA seq libraries were generated with maternal serum specimens that were obtained during 20-to-40-weeks of gestation. Bivariate biomarkers were developed from multiple ex-miRNA pair ratios that served as the biomarkers. The evaluation process determined 110 bivariate ex-miRNA biomarkers for both discovery (48 cases and 34 controls) and verification (23 cases and 18 controls). A machine learning approach combined with iterative methods yielded three biomarkers as bivariate pairs of miRNA that managed to distinguish between preeclampsia cases and controls while reaching 93% sensitivity with 55% positive predictive value and clinical PE severity classification. The independent validation study tested 11 PE cases and 7 controls with these three biomarkers obtaining results with 91% sensitivity and 85% positive predictive value. Three bivariate ex-miRNA biomarkers have been identified, tested, and confirmed, which, when applied sequentially, provide precise early detection of preeclampsia.

Ilona Jaszczuk, Dorota Koczkodaj , Adrianna Kondracka et al. (2022) ^[4] The study emphasized miRNA-210's role in pre-eclampsia development. The article drew its conclusions from various studies about how circulating miRNAs function as promising biomarkers to detect human physiological and disease states. The biological advantage of miRNAs lies in their resistance to degradation in bodily fluids including serum alongside the accessibility of obtaining these samples for analysis using non-invasive procedures. The main origin of miRNA-210 in maternal

serum during pregnancy comes from the placenta although damaged endothelium should be included as a potential source. Serum from pregnant women who develop clinical pre-eclampsia symptoms shows increased levels beginning at week 8 and extending to week 12 before delivery. Study findings show that miRNA-210 functions well as a potential biomarker tool for predicting pre-eclampsia onset during pregnancy.

Deeba S. Jairajpuri, Zainab H. Malalla, Sameh Saray et al. (2021)^[77]; Between November 2017 and January 2018 case-control study was done which included 30 Arab women diagnosed with PE—15 were classified as having mild PE and 15 as having severe PE along with 15 healthy pregnant women. The study analyzed possible hypoxia-mediated pathological pathways involved in pre-eclampsia development. miRNA-210 plasma expression levels in patients were examined of severe PE and mild PE then assessed how altered relative expression influences target gene differential expression between both groups. Both groups (mild PE and severe PE) showed statistically significant relative expression compared to controls using P-values below 0.01 and fold changes higher than 2 as established cutoff criteria. All severe PE patients showed higher miR-210 expression compared to mild PE patients as their relative expression was measured at 19.20 (P value = 0.003) and 10.43 (P value = 0.005), respectively. The study results show that preeclampsia patients exhibit higher miRNA-210 levels than patients without preeclampsia.

Yousra M. Mammdoh, Omar, Hanan et al. (2021)^[78] ; A prospective cohort study was conducted in Assiut University hospital, Egypt. The study analyzed plasma samples of 40 pregnant women during a period between December 2018 to March 2020 with gestational ages ranging from 14 to 26 weeks who had several risk factors for preeclampsia. Pregnant women with preeclampsia showed increased plasma levels of miRNA-210 when compared to those who did not develop PE. Plasma levels of miRNA-210 demonstrate potential value for predicting preeclampsia onset in high-risk pregnant women. Q-PCR technique was used to measure miRNA-210 concentrations within plasma samples. The investigation followed pregnant patients through antenatal clinic appointments to assess predicted PE outcomes in the study population. Plasma miRNA-210 showed substantial elevation among pregnant women with pre-eclampsia (PE) risk factors who developed PE after follow-up [mean $\pm$ SE (19.23 ± 6.95)], with a median of 15.48 versus those without PE [mean $\pm$ SE (4.29 ± 1.36)], with a median of 1.51 ($P = 0.001$). The ROC curve helped determine the predictive power of miRNA-210 for pre-eclampsia diagnosis in pregnant women exhibiting risk factors. With a 2.28-fold change cutoff plasma miRNA-210 achieved an 87.5% sensitivity combined with 68.8% specificity for preeclampsia prediction in at-risk pregnant patients as measured by the area under the curve (AUC) of 0.852.

Fetnat M. Tolba, Adel Agha, Maha Rachwan et al (2020)^[79]; A study conducted at Benha University, Egypt throughout 2018-2019 demonstrated that pre-eclampsia patients exhibit higher miRNA-210 in their plasma and this increase is more significant in severe pre-eclampsia than in moderate pre-eclampsia cases. The analysis of serum miRNA-210 stands as a non-invasive tool for detecting pre-eclampsia in pregnant women and predicting its development. The study examined 30 pregnant women with preeclampsia in which Group I contained 15 mild cases

and Group II contained 15 severe cases. The analysis included 20 healthy pregnant women who matched the study participants in terms of age and sex. Women participating in this study received extensive medical history evaluation and complete health examinations and laboratory testing and gene analysis for miRNA-210 through RT-PCR. Serum miRNA-210 levels surged markedly higher in pre-eclampsia patients compared to controls (P value <0.001) and severity of pre-eclampsia directly correlated to raised miRNA levels (P value <0.001). miRNA 210 displayed robust positive connections to blood pressure readings and proteinuria and both AST and ALT concentrations showed significance as well (P value 0.002). The research showed a positive relationship along with statistical significance (P value 0.002) between miRNA-210 and the values for AST and ALT and PTT. The diagnostic accuracy of PE reached 90.0% sensitivity and 85.0% specificity according to this study's results.

Andrea Hornakova, Zuzana Kolkova, Veronika Holubekova et al (2020)^[80] , Slovakia, published a research article on Diagnostic Potential of miRNAs as the Biomarkers in Detection of PE. Studies confirmed that women with preeclampsia presented elevated levels of miRNA-210 and miRNA-182. Regressive research studies on preeclampsia women have focused on two key microRNA elements: miRNA155 and miRNA-210. Increased levels of miRNA-210 were found in preeclampsia patients which generated trophoblast inhibition and limited migration and invasion capabilities. The blood testing of miRNA210 revealed increased expression in both placenta and patient plasma samples from preeclampsia cases. To clarify miRNA function as disease biomarkers new experimental strategies must emerge and acquired experimental findings must link with database records and

computational prediction assets to reveal miRNA activities across medical conditions while selecting appropriate biomarkers.

Mehdi Koushki, Nasrin Amiri Dash Atan, Hossein Omid-Ardali et al. (2018)

^[70] have done a meta-analysis search strategy on evaluation of the relationship between miRNA-210 expression and risk of pre-eclampsia. The analysis used a fixed-effect model which showed absence of heterogeneity. They identified 12 studies on PE that reported alterations in miRNA-210 levels. The PE and control groups comprised 238 and 277 participants. The standardized mean differences (SMDs) for miRNA-210 levels were evaluated, resulting in an SMD of 0.32, a 95% confidence interval of 0.14 to 0.49, and a p-value 0.97. The results suggested the expression level of miRNA-210 could serve as a predictive marker and a diagnostic tool for pre-eclampsia.

Lu Gan, Zheng Liu, Ming Wei et al. (2017) ^[81]; A case-control investigation performed between November 2015 and October 2016 on 40 pregnant women at the First Affiliated Hospital of Jinan University in China demonstrated an association between preeclampsia development and elevated serum levels of miRNA-210 and miRNA-155. The observed findings present potential novel methods to determine PE risk among pregnant women. Research findings throughout the past decades demonstrate that microRNA molecules play critical roles in the pathophysiology of PE. The exact mechanisms that drive PE development remain a unclear matter. Comparative genetic expression of four microRNAs (microRNA-210, microRNA-155, microRNA-125b-5p, and microRNA-125a-5p) in 20 pregnancies with preeclampsia versus 20 normotensive pregnancies. Both population cohorts

underwent Ct level assessment through real-time quantitative reverse transcriptase polymerase chain reaction methodology. The research showed elevated microRNA210 and microRNA155 levels in preeclampsia-affected pregnancy patients. The diagnostic testing showed AUC results at 0.750 for miRNA-210 evaluation and 0.703 for microRNA-155 assessment. The values for AUC regarding microRNA-210 (serum/urine ratio) and AUC for microRNA-155 (serum/urine ratio) reached 0.761 and 0.718. A positive relationship existed between 24hour urine protein concentrations and urinary levels of both microRNA-210 and microRNA-155. The research shows serum microRNA-210 along with microRNA-155 establishes both sensitivity and specificity for diagnosing PE in pregnant patients. The discovered miRNAs serve as promising diagnostic tools to detect women who may develop PE.

Pooneh Nikuei, Nahid Davoodian, Iman Tahamtan et al. (2015)^[82]; A systematic electronic search of observational studies including cohort, case-control alongwith cross-sectional studies was conducted through Pubmed, Embase, Web of Science, Scopus and Cochrane and OvidSP MEDLINE along with LILACS. According to the study, miRNAs gained considerable attention as potentially new diagnostic biomarkers for pre-eclampsia (PE), tissue damage, and cancer. According to recent reports, preeclamptic patients' serum and placenta exhibit aberrant miRNA expression. miRNA-210 emerges as the most prevalent placental miRNA during preeclampsia because it functions as a hypoxia-responsive microRNA. Across all cell types, miRNA-210 levels increase in response to low oxygen availability, and they are elevated in hypoxia-related conditions such as PE and cancer. The specific microRNAs discovered possess potential value as tools to determine women who may develop PE.

Qian Li, Anxiong Long, Liansheng Jiang et al. (2015)^[83]; A case-control study at Shanghai First People's Hospital in China involved 64 female participants to measure ten distinctive placental miRNAs while assessing their diagnostic potential for early PE detection. The study demonstrates that miRNA-210 and two other miRNA types present elevated levels in preeclampsia affected mothers starting at 20 weeks of pregnancy that continue through the third trimester versus healthy controls. Their study involved measuring ten placenta-derived distinctive microRNAs in blood samples because these microRNAs might help diagnose preeclampsia at an early stage. The investigation analyzed ten microRNAs showing differential expression patterns with four elevated microRNAs (microRNA-152, microRNA-182, microRNA-183, and microRNA-210) and six reduced microRNAs (microRNA-1, microRNA-328, microRNA-363, microRNA-377, microRNA-500, and microRNA-584). The levels of miRNAs (microRNA-152, microRNA-183, and microRNA-210) increase from the 20th to 24th gestational weeks and indicate future risk of developing preeclampsia. The AUC for PE prediction from the 20th to 24th gestational weeks using microRNA-152, microRNA-183, and microRNA-210 was determined at 0.94, 0.97 and 0.93 respectively. Pregnant women with preeclampsia exhibit elevated levels of circulating microRNA-152, microRNA-183, and microRNA-210 as detected in the second trimester which enables effective early differentiation between patients at preeclampsia risk and those with normal pregnancy progress 8-10 weeks before clinical manifestations emerge.

Blendi Ura, Giordana Feriotto, Lorenzo Monasta et al. (2014)^[84]; Retrospective study evaluated miRNA patterns in serum specimens taken from pregnant subjects between weeks twelve and fourteen to determine those who later developed severe PE in their final trimester. The results were compared against samples from healthy pregnancy patients. 19 differentially expressed miRNAs were identified, comprising 12 upregulated (miRNA-1233; miRNA-650; miRNA-520a; miRNA-215; miRNA-210; miRNA-25; miRNA-518b; miRNA-193a-3p; miRNA-32; miRNA-204; miRNA-296-5p; miRNA-152) and 7 downregulated (miRNA-126; miRNA-335; miRNA-144; miRNA-204; miRNA-668; miRNA-376a; miRNA-15b) in severe PE, utilizing TLDA chips (human microRNA panel V3.0). 4 miRNAs (miRNA-1233, miRNA-520a, miRNA-210, miRNA-144) were confirmed in severe PE serum samples using Quantitative Reverse Transcription Polymerase Chain Reaction. (qRT-PCR).

Lauren Anton, Anthony O. Olarerin-George, Nadav Schwartz et al. (2013)^[81]; The Hospital of the University of Pennsylvania in Philadelphia conducted two clinical studies using 72 women in a case-control design and 96 women in a prospective cohort design to evaluate miRNA-210 expression. The research shows miR-210 measurement serves as a reliable biological indicator to identify women at risk for developing hypertensive pregnancy complications before disease symptoms emerge. A case-control study analyzed serum miRNA210 expression levels from maternal blood during clinical preeclampsia diagnosis. Study showed HDP development in women led to elevated miR-210 levels which reached 5.3 times the original expression compared to women who did not develop HDP ($P = 0.003$). Higher miR-210 expression levels led to HDP development by 1.8 times more than normal (95% CI 1.3 to 2.6; $P = 0.001$). Among the risk factors including race,

tobacco use and BMI and parity level each five-unit increase of miR-210 boosted the likelihood of HDP by a factor of 2.7 (95% CI 1.6 to 4.6; $p < 0.0001$). The analysis of women with preeclampsia achieved a fourfold rise in preeclampsia risk assessment (95% CI 1.8 to 8.7; $p < 0.0001$; AUC 0.89) by demonstrating higher miR-210 expression.

Michal A Elovitz, Anthony Olarein George, Jamie Bastek et al. (2012)^[86]; Two independent research groups were studied in Philadelphia. The first dedicated their study to case-control analysis with 42 participants and their second research section used prospective cohort evaluation with 38 women in their sample. This study aimed to establish specific miRNAs as biomarkers for detecting preeclampsia in advance through analyzing miRNA210 which provides predictive power for the condition months before clinical diagnosis. These results support miRNA210 as an ideal diagnostic tool and surveillance marker for pre-eclampsia assessment through future intervention trials. The observed miRNA210 value variations showed statistical distinctions between preeclampsia patients and healthy controls ($P = 0.0009$). The risk for developing pre-eclampsia escalated by 5.5 times at each stage of miRNA210 level increase (1.7-17.9, $P 0.005$). The diagnostic value of miRNA210 indicated an AUC rate of 0.83 alongside 95% sensitivity while maintaining 50% specificity. The positive likelihood ratio stands at 8.5 when the test shows a 60% sensitivity level. The median levels of miRNA210 demonstrated significant variations between pre-eclampsia-developing and non-pre-eclampsia women in samples from the second trimester ($P 0.0003$). ANOVA results showed an ROC value of 0.85 together with 90% sensitivity which produced 84% specificity and a Likelihood Ratio measurement of 5.7. The study aimed to understand if specific miRNAs could serve as biomarkers to identify and predict pre-eclampsia.

METHODS AND MATERIALS

SOURCE OF DATA:

Patients who delivered at B.L.D.E (Deemed to be University), Shri B.M. Patil Medical College Hospital and Research Centre, Vijayapura.

- ⇒ Health care setup: Tertiary care hospital
- ⇒ Total Sample size: 102 pregnant women (51 cases and 51 controls)
- ⇒ Type of study: Case - Control Study
- ⇒ Study Period: April 2023 - February 2025

INCLUSION CRITERIA:

Pregnant women age ≥ 18 years with Singleton pregnancy.

- ⇒ Prenatal care at BLDE.
- ⇒ Adverse outcomes if any, in the mother and fetus shall be recorded.

➤ **CASES:**

- ⇒ A pregnant woman with elevated BP readings of $\geq 140/90$ mmHg measured twice during a six-hour period while exhibiting significant proteinuria (either ≥ 300 mg through 24-hour urine analysis or $\geq 1+$ by dipstick) following 20 weeks period of pregnancy, in a previously normotensive woman.

➤ **CONTROLS:**

- ⇒ The normotensive pregnant women of BP $< 140/90$ mmHg on at least two separate antenatal visits, 2 to 4 weeks apart with no proteinuria.

EXCLUSION CRITERIA:

- ⇒ Any congenital fetal malformations or chromosomal abnormalities
- ⇒ Chronic Hypertension
- ⇒ Twins with PE
- ⇒ Renal disease with PE
- ⇒ Cardiac disease with PE
- ⇒ Recent infection
- ⇒ APLA Syndrome

SAMPLE SIZE CALCULATION: 102

With anticipated sensitivity and specificity of miRNA in preeclampsia at 90.0% and 85%, respectively ^[79], considering the prevalence of preeclampsia at 4.6% ^[87], at the precision of 10% and 95% confidence, the required sample size was 51 per group. (Total sample size - 102 considering equal size groups)

The formula used is -

$$N = \frac{Z^2 P(1-p)}{\Delta^2}$$

N will be (a+c) if we use sensitivity as p

$$N = (a+c)/\text{Prevalence}$$

STATISTICAL ANALYSIS:

- ⇒ The analysis was conducted through SPSS version 20 statistical software brand SPSS, Inc. from Chicago, IL.
- ⇒ The obtained data was entered into a Microsoft Excel sheet followed by analysis utilizing statistical package for social sciences (version 20).
- ⇒ Results were shown through Mean/Median $\pm$ SD measurements together with counts, percentages and diagrams.
- ⇒ The data analysis employed the Mann-Whitney U test to evaluate not normally distributed variables. A Chi-Square test evaluated the statistical relationships between categorical variables within the two tested groups.
- ⇒ Mann-Whitney U test was applied to compare the miRNAs expression levels.
- ⇒ Spearman's correlation "r" determined relationships between miRNA-210 and other variables within a range of -1 to +1.
- ⇒ A p value below 0.05 establishes statistical significance for this study. All the tests performed were two-tailed in all cases.
- ⇒ ROC analysis was done to evaluate pre-eclampsia using miRNA-210 while calculating the best cutoff point along with diagnostic indices that produced sensitivity, specificity, positive predictive value and negative predictive value.

METHODOLOGY AND SAMPLE COLLECTION:

Institutional review board approval was sought [BLDE(DU)/IEC/891/2022-23].

Informed and written consent was obtained following the Declaration of Helsinki once the patient was admitted. The study had been registered with the Clinical Trials Registry of India (CTRI/2023/10/059019).

Pre-eclamptic patients who met the inclusion criteria and provided consent were recruited as cases, while normotensive pregnant women who gave their consent served as controls. Both the cases (pre-eclamptic women) and control (normotensive women) group were matched with age $\pm$ 5years, period of gestation $\pm$ 1 week, and obstetric score.

All the women included during this study are subjected to:

- ⇒ Complete history taking, including personal information on the patient and the maternal age, obstetric history, significant family history, period of gestation, and preeclampsia onset.
- ⇒ Clinical Examination includes- General physical examination and clinical assessment – Systolic Blood Pressure, Diastolic Blood Pressure, pedal edema, Weight, Body mass index (BMI), Obstetric examination.
- ⇒ Laboratory investigations – Renal Function Test, Complete Blood Count, Liver Function Test, Coagulation Profile, Fundoscopy
- ⇒ Obstetrics Growth Scan with Doppler
- ⇒ Follow-up of cases will be done till delivery.
- ⇒ Information will be collected from each patient through a pre-tested proforma meeting the study's objectives.

⇒ Three millilitres of blood was drawn, and the serum has been extracted and divided into portions before being collected. The serum aliquots were frozen at 80°C.

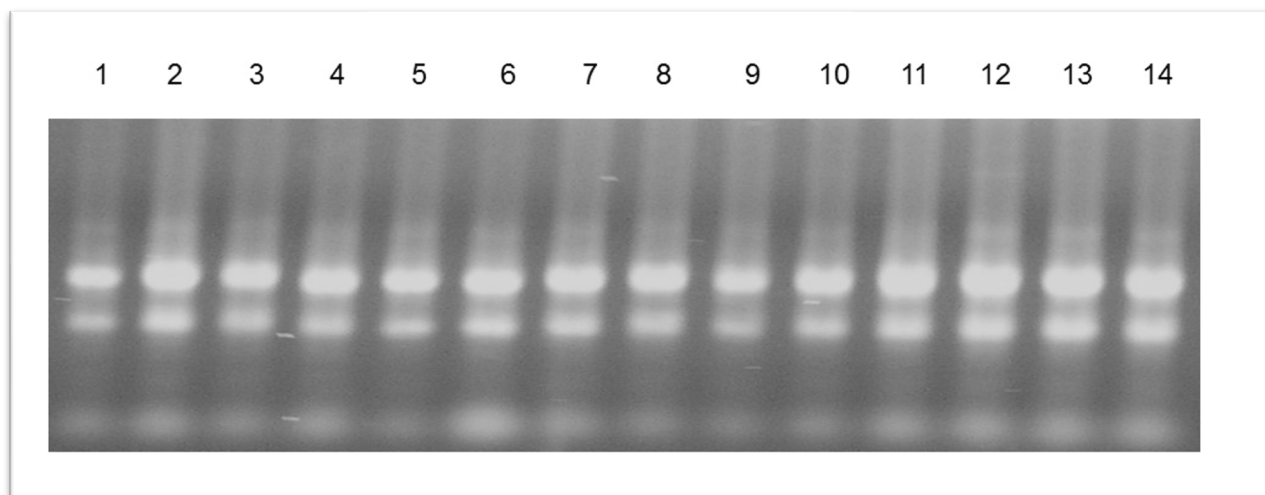
⇒ The process of obtaining serum requires centrifugation at 1600 rpm for 15 minutes under room temperature conditions. The supernatant from the isolation process was deposited into Eppendorf tubes. Recentrifuging at 14,000 rpm for 10 min allowed the separation of cell debris while the collected supernatants underwent storage at 80 °C prior to RNA extraction.

MOLECULAR ANALYSIS:

⇒ RNA EXTRACTION:

The Nucleospin Plasma isolation Kit extracted RNA from 200µl serum which was recorded on the teckon make multimode plate reader at 260/280 OD to check RNA purity and reached concentrations ranging from 0.25–8 µg.

(Figure 12) Image depicting of Total RNA



⇒ **POLYADENYLATION AND REVERSE TRANSCRIPTION:**

The cDNA synthesis reaction was set up for each of the RNA sample to enable qPCR analysis. The absolute quantity of miRNA levels can be measured through a standard curve.

- The following reagents were mixed in an RNase-free 0.2 ml tube:

⇒ **POLY(A)/cDNA SYNTHESIS REACTION: (Table -5)**

Reagent	Volume(μ l)
mRQ Buffer (2x)	5
RNA sample (0.25–8 μ g)	3.75
mRQ Enzyme	1.25
Total Volume	10

- The thermal cycler incubated reactions at 37°C for one hour using its temperature programs then shifted to 85°C for five minutes to deactivate enzymes.
- Each tube received 90 μ l ddH₂O to reach a total volume of 100 μ l.
- This prepared cDNA solution was used for miRNA quantification procedures.

⇒ **QUANTIFICATION OF miRNA BY qPCR:**

Standard curve method enabled the procedure. Two extra qPCR amplifications were performed using U6 snRNA controls for $\Delta\Delta$ Ct analysis and cDNA from synthetic miRNA for standard curve analysis.

⇒ **SAMPLE qPCR REACTION: (Table- 6)**

REAGENT	VOLUME(μ l)
ddH ₂ O	9
TB Green Advantage Premix (2X)	12.5
ROX Dye (50X)	0.5
miRNA-specific primer (10 μ M)	0.5
mRQ 3' Primer (10 μ M)	0.5
cDNA	2.0
Total volume	25

⇒ **U6 qPCR REACTION: (Table- 7)**

REAGENT	VOLUME(μ l)
ddH ₂ O	9
TB Green Advantage Premix (2X)	12.5
ROX Dye (50X)	0.5
U6 Forward primer (10 μ M)	0.5
U6 Reverse Primer (10 μ M)	0.5
cDNA	2.0
Total volume	25

The reactions were cycled using the instructions described by TAKARA Make single sep QRT-PCR for real-time kit. ABI QUANT 5 Studio instrument was utilized for this procedure.

• Denaturation 95°C 10 seconds • qPCR x 40 Cycles • 95°C for 5 seconds • 60°C for 20 seconds	• Dissociation Curve • 95°C for 60 seconds • 55°C for 30 seconds • 95°C for 30 seconds
---	---

⇒ **DELTA-DELTA CT ($\Delta\Delta C_t$) METHOD:**

The delta-delta Ct ($\Delta\Delta C_t$) technique probes relative miRNA quantities in different samples by aligning them against U6 RNA for normalization purposes. The Ct values were calculated by analyzing the unknown miRNA together with the reference U6 RNA in each tested sample. The relative levels were calculated through the $\Delta\Delta C_t$ method assessment following this measurement process.

⇒ **ABSOLUTE QUANTIFICATION METHOD (STANDARD CURVE):**

A calibrated synthetic miRNA preparation provides the basis for preparing serial dilutions to create the standard curve. The Ct values obtained during the experiments serve as input for determining miRNA copy number through the established plot.

- A logarithmic scale plot was used to display Ct data from duplicate qPCR runs of cDNA derived from synthetically diluted miRNA samples along with their corresponding input miRNA copy numbers. (Step 1)

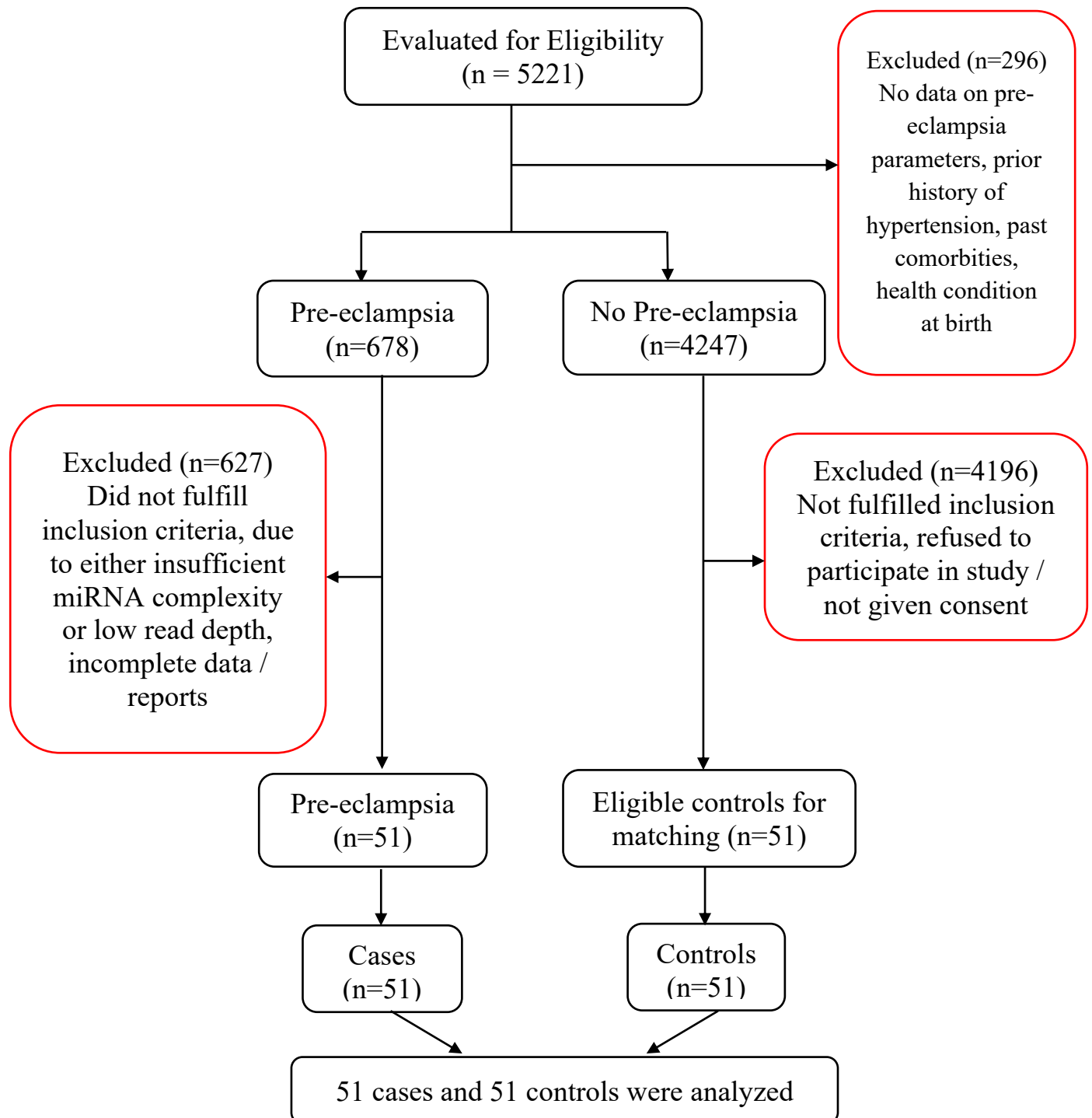
- Using the standard curve established in Step 1 corresponding RNA copy numbers were calculated by retrieving data from each duplicate experiment's average Ct values.

RESULTS

PARTICIPANTS:

A total of 5,221 women delivered at Shri B M Patil Medical College Hospital & Research Centre, Vijayapura from April 2023 to February 2025. 102 consenting women are taken into this study who fulfilled the inclusion criteria.

(Figure -13) Flowchart of participant recruitment in case-control study



GENETIC ANALYSIS:

The peripheral venous blood of the 102 patients who were enrolled in the study was collected and sent for genetic analysis of the miRNA-210 gene. The miRNA-210 gene was analyzed in both the groups and the results are as follows:

(Table - 8) Quantification of RNA by Multimode Reader

SI No.	RNA Samples of Cases	OD at 260/280	Concentration in ng/ml	SI No.	RNA Samples of Cases	OD at 260/280	Concentration in ng/ml
1	Case 1	1.94	55	27	Case 33	1.91	78.50
2	Case 2	1.87	66	28	Case 34	1.87	84.03
3	Case 7	1.90	75.03	29	Case 35	1.96	90.02
4	Case 8	1.92	97	30	Case 36	2.03	49
5	Case 9	1.87	92	31	Case 37	2.01	68
6	Case 10	2.01	75	32	Case 38	2.03	73
7	Case 11	2.09	85.01	33	Case 39	1.88	95
8	Case 12	1.92	93	34	Case 40	2.05	62
9	Case 13	1.96	90	35	Case 41	1.91	81
10	Case 14	2.02	88	36	Case 42	1.92	93
11	Case 15	2.04	71	37	Case 43	1.98	76
12	Case 16	2.05	62.90	38	Case 44	2.01	82
13	Case 17	1.91	85.5	39	Case 45	1.93	75
14	Case 18	1.98	100	40	Case 46	1.95	88
15	Case 19	2.06	74.80	41	Case 47	2.04	91
16	Case 20	1.98	82	42	Case 49	2.02	73
17	Case 21	1.89	61	43	Case 50	1.90	57
18	Case 22	2.04	97	44	Case 51	1.95	60.50
19	Case 23	2.07	58.05	45	Case 52	1.93	89
20	Case 24	1.95	64	46	Case 53	1.99	91
21	Case 25	1.90	57	47	Case 55	2.02	72
22	Case 26	1.93	94	48	Case 57	1.93	77
23	Case 27	1.92	62	49	Case 60	2.05	94
24	Case 28	1.98	98	50	Case 61	2.01	82

25	Case 29	2.03	94	51	Case 62	1.97	85.70
26	Case 30	1.98	91				
SI No.	RNA Samples of Controls	OD at 260/280	Concentration in ng/ml	SI No.	RNA Samples of Controls	OD at 260/280	Concentration in ng/ml
1	Control 3	1.90	71	27	Control 78	1.89	97
2	Control 4	2.06	82	28	Control 79	1.91	49
3	Control 5	1.92	89.02	29	Control 80	1.95	61.02
4	Control 6	2.00	76.05	30	Control 81	1.93	73
5	Control 31	1.91	78.01	31	Control 82	1.91	44
6	Control 32	1.92	72	32	Control 83	2.02	68.01
7	Control 48	1.94	80	33	Control 84	2.05	84.02
8	Control 54	1.91	49.02	34	Control 85	1.92	76
9	Control 56	2.01	93	35	Control 86	1.90	48
10	Control 58	2.05	85	36	Control 87	1.94	52
11	Control 59	2.02	96	37	Control 88	2.01	81
12	Control 63	1.92	74	38	Control 89	2.03	72.05
13	Control 64	1.98	82	39	Control 90	2.07	82.02
14	Control 65	1.87	91	40	Control 91	1.96	67
15	Control 66	2.03	75.30	41	Control 92	1.94	69.01
16	Control 67	2.06	57.01	42	Control 93	1.92	57
17	Control 68	1.94	77	43	Control 94	1.91	86
18	Control 69	1.96	84	44	Control 95	1.93	63.05
19	Control 70	2.01	82	45	Control 96	1.95	74.02
20	Control 71	2.03	70.01	46	Control 97	2.01	61
21	Control 72	1.93	78	47	Control 98	2.03	88
22	Control 73	1.90	58.04	48	Control 99	2.04	51.10
23	Control 74	2.05	82	49	Control 100	1.92	66
24	Control 75	1.95	79	50	Control 101	1.95	72.04
25	Control 76	2.06	64.03	51	Control 102	2.04	89
26	Control 77	2.01	68				

Table 8 presents the results of RNA quantification using a multimode reader, indicating the quantity of RNA in each sample. The measurements were taken at the 260/280 optical density ratio, specific for nucleic acids.

(Table - 9) Table showing miRNA-210 ($2^{\Delta\Delta Ct}$ expression) levels via RT-PCR in both study groups

SAMPLE NO.	CONDITION	miRNA210 $2^{\Delta\Delta Ct}$
1	Case	33.2338916
2	Case	13.15464126
3	Control	0.093051078
4	Control	0.416821038
5	Control	0.006247523
6	Control	2.052667568
7	Case	24.3778671
8	Case	15.11071477
9	Case	15.21581811
10	Case	46.35275981
11	Case	36.36763824
12	Case	12.70654589
13	Case	10.10852083
14	Case	23.71125304
15	Case	28.93178305

Table 9 represents fold change in the expression levels of miRNA-210 in both study groups. (fold change = $2^{\Delta\Delta Ct}$)

SAMPLE NO.	CONDITION	miRNA210 2⁻ - ΔΔCt	SAMPLE NO.	CONDITION	miRNA210 2⁻ - ΔΔCt
16	Case	12.61877536	42	Case	53.24533894
17	Case	23.66336491	43	Case	42.35860972
18	Case	17.23775513	44	Case	26.25614731
19	Case	13.43104823	45	Case	18.69503586
20	Case	22.43221225	46	Case	22.40890113
21	Case	36.44123631	47	Case	38.70862975
22	Case	27.20877312	48	Control	0.013089768
23	Case	28.76016405	49	Case	31.91140004
24	Case	36.40336729	50	Case	39.79687746
25	Case	30.40001225	51	Case	13.32441233
26	Case	37.94926398	52	Case	41.20031131
27	Case	13.5104142	53	Case	18.71340262
28	Case	26.62266947	54	Control	0.171248905
29	Case	31.03878113	55	Case	20.31654722
30	Case	19.22062486	56	Control	0.449845033
31	Control	0.0071105	57	Case	21.32661857
32	Control	9.155148792	58	Control	0.003836926
33	Case	16.98277134	59	Control	4.129594142
34	Case	24.01726556	60	Case	26.99430809
35	Case	41.77544622	61	Case	22.40890113
36	Case	26.46474779	62	Case	18.69503586
37	Case	18.05821431	63	Control	2.050534476
38	Case	12.4321163	64	Control	0.131632107
39	Case	22.10039117	65	Control	0.044117657
40	Case	23.52299738	66	Control	0.822165079
41	Case	18.45576968	67	Control	3.744007522

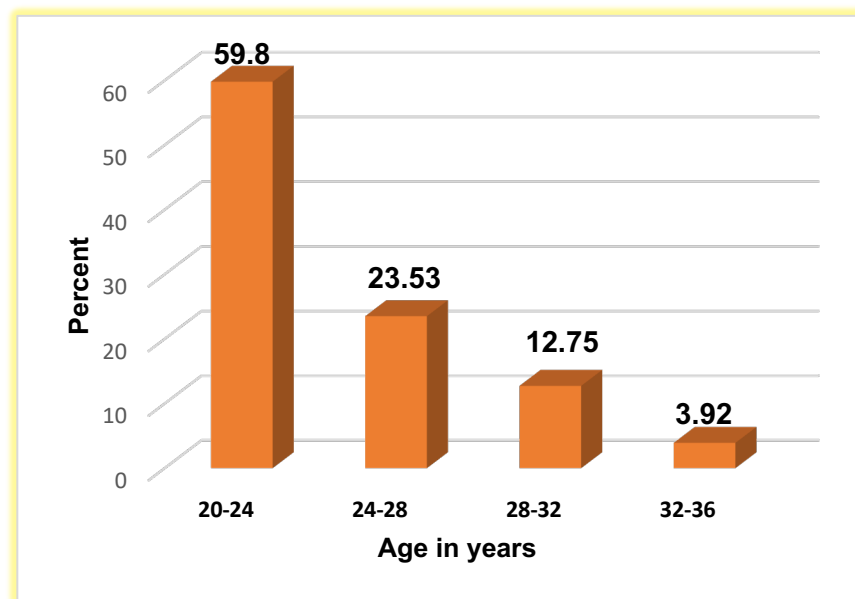
68	Control	3.108029075	86	Control	1.555631119
69	Control	0.001457286	87	Control	0.9474
70	Control	0.173840163	88	Control	6.518695714
71	Control	0.93600188	89	Control	0.019978379
72	Control	0.006283714	90	Control	0.008341851
73	Control	0.000398214	91	Control	6.518695714
74	Control	0.725727578	92	Control	4.300735281
75	Control	2.16970665	93	Control	4.040638635
76	Control	1.236275261	94	Control	3.641627439
77	Control	0.205303956	95	Control	0.446737727
78	Control	2.958433227	96	Control	0.296187638
79	Control	0.657927263	97	Control	0.396277602
80	Control	0.437038819	98	Control	13.21938663
81	Control	16.5164684	99	Control	0.06183568
82	Control	2.259494429	100	Control	0.06183568
83	Control	0.006884177	101	Control	1.010159659
84	Control	5.921653192	102	Control	0.056117064
85	Control	1.019244379			

DESCRIPTIVE DATA:

DISTRIBUTION OF STUDY POPULATION BASED ON AGE:

Among the 102 patients enrolled, majority of the study population (59.8%) belonged to the age group of 20-24 years, 24 patients (23.53%) belonged to 24-28 years, while 12.75% were in the age group of 28-32 years, and 4 (3.92%) in the age group of 31-36 years. The mean age group of our study population in Group 1 was 24.55 ± 4.42 and Group 2 was 23.75 ± 3.70 years. This distribution indicates that our study primarily involved younger individuals, with fewer participants in the older age group.

(Figure -14) showing Distribution of study population based on age

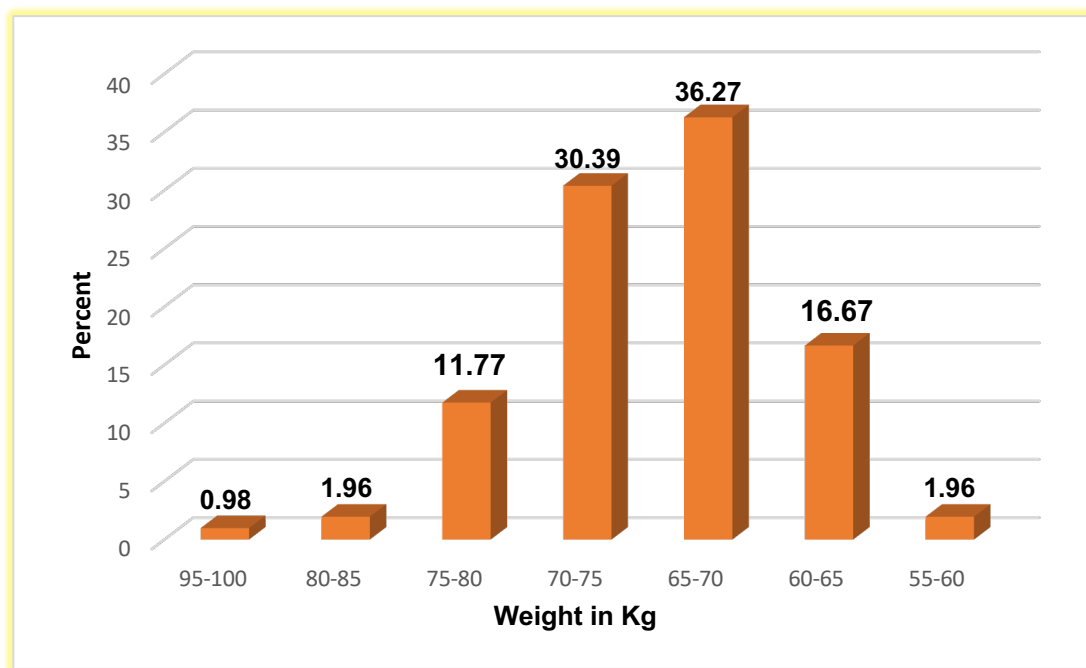


(Table- 10) Table showing distribution of study population based on age

Age in years	Frequency	Percent
20-24	61	59.8
24-28	24	23.53
28-32	13	12.75
32-36	4	3.92
Total	102	100

DISTRIBUTION OF WEIGHT OF THE STUDY POPULATION:

The weight distribution among study participants, as shown in Table 11, that the highest proportion of individuals (36.27%) had a weight between 65-70 kg, followed closely by 30.39% in the 70-75 kg range. Participants weighing 60-65 kg accounted for 16.66%, while 11.76% were in the 75-80 kg category. Only a small percentage of participants fell within the 55-60 kg (1.96%), 80-85 kg (1.96%), and 95-100 kg (0.98%) weight ranges. This distribution indicates that the majority of participants had a weight between 65-75 kg.

(Figure 15) Distribution of weight of the study population***(Table- 11) Table showing distribution of study population based on weight***

Weight in Kg	Frequency	Percent
55-60	2	1.96
60-65	17	16.67
65-70	37	36.27
70-75	31	30.39
75-80	12	11.77
80-85	2	1.96
95-100	1	0.98
Total	102	100

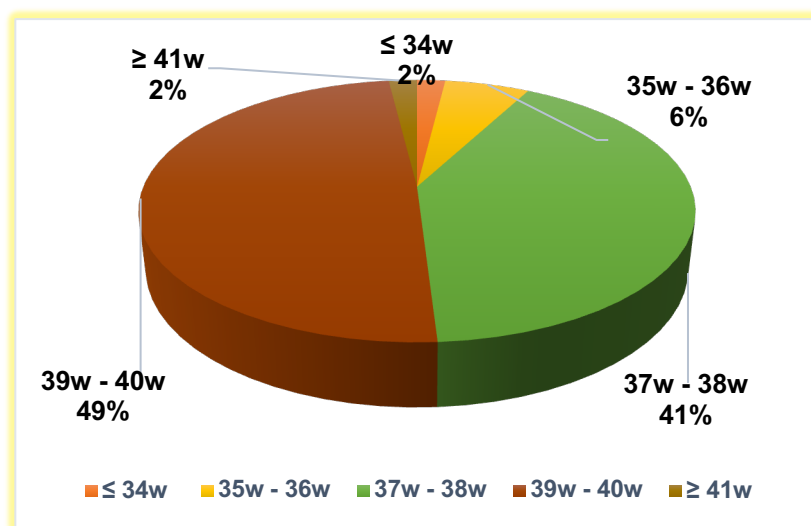
DISTRIBUTION OF PERIOD OF GESTATION AMONG THE STUDY POPULATION:

All the patients enrolled in the study were of the gestational age more than 37 weeks. However, majority of the population (50 patients), were of the gestational age of more than 39 - 40 weeks.

(Table- 12) Table showing distribution of study population based on period of gestation

Period of gestation	Frequency	Percent
≤ 34w	2	1.96
35w - 36w	6	5.88
37w - 38w	42	41.18
39w - 40w	50	49.02
≥ 41w	2	1.96
Total	102	100

(Figure 16) Distribution of period of gestation among the study population



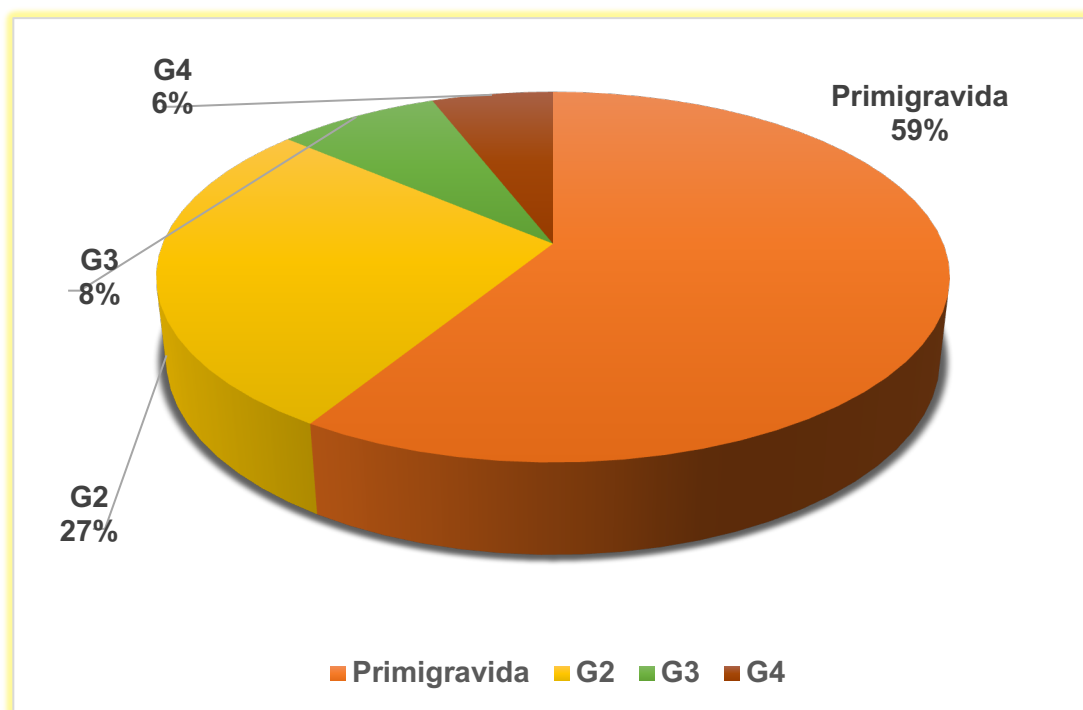
DISTRIBUTION OF PARITY STATUS AMONG THE STUDY POPULATION:

Our analysis shows the distribution of different parity groups (G1-G4) across the two study categories. Each group is evenly distributed, with 50.0% of participants in each group falling into either category 1 or 2. The majority of participants (60 out of 102, 58.83%) belong to Group 1, followed by 28 participants (27.4%) in Group 2, 8 participants (7.84%) in Group 3, and 6 participants (5.9%) in Group 4. This balanced distribution suggests that the intervention categories were equally represented within each group.

(Table- 13) Table showing distribution of study population based on parity status

	Cases	Controls	Total	Percent
PRIMIGRAVIDA	30	30	60	58.83
G2	14	14	28	27.45
G3	4	4	8	7.84
G4	3	3	6	5.88
Total	51	51	102	100

(Figure 17) Distribution of parity status among the study population



OUTCOME DATA AND MAIN RESULTS:

(Table - 14) Table showing comparison of clinical and lab data between the studied groups

Variables		Cases(n = 51)	Controls (n = 51)	P value
Maternal age (Years)	Mean $\pm$ SD	24 $\pm$ 4	23 $\pm$ 3	0.0322*
Gestational age (wks.)	Mean $\pm$ SD	38 $\pm$ 1	38 $\pm$ 1	0.089
Body Mass Index(kg/m ²)	Mean $\pm$ SD	27.9 $\pm$ 2.2	28 $\pm$ 1.6	0.996
Parity state	PG (n%)	30 (58.82)	30 (58.82)	0.50
	MG (n%)	21 (41.17%)	21 (41.17)	
Hemoglobin (gm/dl)	Mean $\pm$ SD	11.4 $\pm$ 1.7	11.3 $\pm$ 1.2	0.743
Platelets (10x3/microL)	Mean $\pm$ SD	229 $\pm$ 93	236 $\pm$ 71	0.672
INR	Mean $\pm$ SD	0.84 $\pm$ 0.10	0.83 $\pm$ 0.06	0.502
Urea (mg/dl)	Mean $\pm$ SD	18.10 $\pm$ 7.2	17 $\pm$ 3.9	0.344
Creatinine (mg/dl)	Mean $\pm$ SD	0.57 $\pm$ 0.16	0.58 $\pm$ 0.14	0.754
miRNA-210 (fold)	Mean $\pm$ SD	25.41 $\pm$ 10.13	2.05 $\pm$ 3.35	< 0.001

The results from the Mann-Whitney U test showed considerable differences between two study groups across various factors. Group 1 (cases) showed a substantial increase in miRNA-210 expression reaching statistical significance ($p < 0.001$) which suggests an association with hypertensive conditions.

(Table 14) displays results indicating that no substantial differences with p value >0.05 existed between PE patients (cases) and control group with respective to gestational intervals (p value 0.089), body mass index (p value 0.996) , parity status

(*p* value 0.50), serum urea (*p* value 0.344) , serum creatinine (*p* value 0.754), Hb% levels (*p* value 0.743), platelet counts (*p* value 0.672), and INR (*p* value 0.502) values. Whereas. maternal age shows (*p* value 0.0322) statistically significant in Group 1.

(Table - 15) Table showing comparison of clinical and lab data between the studied groups

Variables		Cases(n = 51)	Controls (n = 51)	P value
SBP (mmHg)	Mean ± SD	155 ± 15.2	114 ± 7	< 0.001
DBP (mmHg)	Mean ± SD	98.8 ± 8.6	72.7 ± 6	< 0.001
MABP (mmHg)	Mean ± SD	117 ± 9.7	86.5 ± 4.6	< 0.001
PTT (Sec)	Mean ± SD	27.3 ± 2.02	25.3 ± 3.04	< 0.001
SGOT (U/L)	Mean ± SD	47.1 ± 115	24.2 ± 5.06	0.041*
SGPT (U/L)	Mean ± SD	32.5 ± 97	19.2 ± 4.1	0.032*
TSB (mg/dl)	Mean ± SD	0.61± 0.41	0.43 ± 0.18	0.008*
Unconjugated (mg/dl)	Mean ± SD	0.39 ± 0.35	0.25 ± 0.14	0.009*
Proteinuria (≥1+ by dipstick method)	Using Chi-square Test	37 (72.54%)	0	< 0.001
Serum Protein (g/dl)	Mean ± SD	6.27 ± 0.73	6.043 ± 0.48	0.009*
Serum Albumin (g/dl)	Mean ± SD	3.04 ± 0.45	3.57 ± 0.56	< 0.001
Serum uric acid (mg/dl)	Mean ± SD	5.61 ± 1.55	4.44 ± 0.93	< 0.001
ALP (U/L)	Mean ± SD	253 ± 92	160 ± 51.96	< 0.001
AG ratio	Mean ± SD	1.02 ± 0.17	0.95 ± 0.12	0.045*
S Phosphorous(mg/dl)	Mean ± SD	4.15 ± 0.61	3.73 ± 0.73	0.002*
S Chloride(mmol/L)	Mean ± SD	110 ± 3.16	104 ± 4.67	<0.001
S Sodium(mEq/L)	Mean ± SD	136 ± 3.40	138 ± 3.35	0.010*

Numerical data was evaluated with Mann Whitney U test. The analysis used the chi-square test for categorical data. Significant statistical results emerged when p value reached <0.05 and highly significant results emerged when p value reached <0.005 .

Blood pressure parameters (SBP, DBP, and MAP) are significantly elevated in (cases) Group 1 (155 ± 15 vs 114 ± 7 , 98 ± 8 vs. 72 ± 6 , 117 ± 9 vs. 86 ± 4), with p value <0.001 , indicating a hypertensive state, whereas (controls) Group 2 exhibits lower values, suggesting better cardiovascular stability. PTT is elevated in cases group than controls (27.3 ± 2.02 sec vs. 25.3 ± 3.04 sec with p value < 0.001).

Biochemical markers, such as serum albumin (3.04 ± 0.45 g/dl vs. 3.57 ± 0.56 g/dl), serum protein (6.27 ± 0.73 g/dl vs. 6.043 ± 0.48 g/dl), proteinuria (using dipstick method), reflecting impaired protein metabolism. uric acid (5.61 ± 1.55 mg/dl vs. 4.44 ± 0.93 mg/dl), Alkaline Phosphatase (253.73 ± 92.10 U/L vs. 160.71 ± 51.96 U/L), are higher in cases having significant p value of <0.001 .

Also, other parameters such as Total Serum Bilirubin (0.61 ± 0.41 mg/dl vs. 0.43 ± 0.18 mg/dl), Unconjugated (0.39 ± 0.35 mg/dl vs. 0.25 ± 0.14 mg/dl), Albumin Globulin ratio (1.02 ± 0.17 vs. 0.95 ± 0.12), S. Phosphorous (4.15 ± 0.61 mg/dl vs. 3.73 ± 0.73 mg/dl), S. Chloride (110 ± 3.16 mmol/L vs. 104 ± 4.67 mmol/L), S Sodium (136 ± 3.40 mEq/L vs. 138 ± 3.35 mEq/L) shows significant p value of 0.008 , 0.009 , 0.045 , 0.002 , 0.001 , 0.010 respectively.

Serum Glutamic-Oxaloacetic Transaminase (SGOT) (47 ± 115 U/L vs. 24 ± 5 U/L) and Serum Glutamic Pyruvic Transaminase (SGPT) (32 ± 97 U/L vs. 19 ± 4 U/L) are also higher in Group 1 (cases) than Group 2 (controls) with p values of <0.041 and 0.032 , overall indicating possible renal and hepatic stress.

(Table - 16) Table showing fetal growth parameters in both study groups

Variables		Cases	Controls	P value
Abdominal Circumference (mm)	Mean $\pm$ SD	318 $\pm$ 18.66	327 $\pm$ 11.04	0.003*
Femur length (mm)	Mean $\pm$ SD	71.25 $\pm$ 3.67	72.59 $\pm$ 2.99	0.047*
Head Circumference(mm)	Mean $\pm$ SD	311 $\pm$ 36.87	324 $\pm$ 9.62	0.012*
MCA	RI (Mean $\pm$ SD)	0.76 $\pm$ 0.13	0.75 $\pm$ 0.60	0.691
	PI (Mean $\pm$ SD)	1.33 $\pm$ 0.26	1.45 $\pm$ 0.22	0.017*
UA	RI (Mean $\pm$ SD)	0.65 $\pm$ 0.10	0.63 $\pm$ 0.06	0.446
	PI (Mean $\pm$ SD)	0.96 $\pm$ 0.28	0.94 $\pm$ 0.10	0.666
Birth weight (kg)	(Mean $\pm$ SD)	2.57 $\pm$ 0.49	2.79 $\pm$ 0.33	0.010*

Mann Whitney U test was used. Significant statistical results emerged when p value reached <0.05 and highly significant results emerged when p value reached <0.005 .

Fetal growth indicators, including head circumference (311.22 $\pm$ 36.87 mm vs. 324.92 $\pm$ 9.63 mm), abdominal circumference (318.20 $\pm$ 18.66 mm vs. 327.41 $\pm$ 11.05 mm), femur length (71.25 $\pm$ 3.67 vs. 72.59 $\pm$ 2.99) with *p value* < 0.05 and birth weight (2.57 $\pm$ 0.49 kg vs. 2.79 $\pm$ 0.34 kg) with *p value* < 0.010 , were significantly better in Group 2, suggesting improved fetal development. Whereas, ultrasound doppler findings (MCA , UA) shows no significant difference.

(Table 14, 15, &16) These findings highlight that Group 1 exhibits more hypertensive and metabolic complications, whereas Group 2 demonstrates better maternal and fetal outcomes, reinforcing the benefits of the intervention.

The observed variations in hematological, biochemical, and Doppler indices indicate that Group 1 may be associated with hypertensive complications and suboptimal fetal outcomes, while Group 2 demonstrates improved maternal and fetal health parameters, likely due to the intervention.

(Table - 17) Table showing correlation coefficient (r) between miRNA-210 and study groups

miRNA-210	r	p value
Maternal age (Years)	0.701	0.487
Gestational age (Weeks)	0.382	0.001
Body Mass Index (kg/m²)	-0.0036	0.720
Systolic blood pressure (mmHg)	0.723	<0.001
Diastolic blood pressure (mmHg)	0.739	<0.001
Mean Arterial Pressure(mmHg)	0.757	<0.001
Hemoglobin (gm/dl)	0.110	0.272
Platelets(10x3/microL)	-0.128	0.198
PT (Sec)	0.512	<0.001
PTT (Sec)	-0.190	0.055
INR	0.181	0.069
Urea (mg/dl)	0.570	<0.001
Creatinine (mg/dl)	0.014	0.893
SGOT (U/L)	0.620	<0.001
SGPT (U/L)	0.650	<0.001
serum Protein	0.674	<0.001
serum Albumin	0.328	0.0008
serum Uric acid	0.532	<0.001
serum ALP	0.460	<0.001

Spearman's correlation was used (r value indicates -1 to +1)

miRNA-210 reveals a statistically significant positive correlation between and gestational age, systolic and diastolic blood pressure, and mean arterial blood

pressure, Prothrombin Time, SGOT, and SGPT, serum urea, protein, albumin, uric acid, and ALP with *r value of 0.382, 0.723, 0.739, 0.757, 0.512, 0.620, 0.650, 0.570, 0.674, 0.328, 0.532, 0.460* respectively.

(Table- 18) Table showing analysis between study groups using Pearson's chi-squared test

VARIABLE		CASES (n=51)	CONTROLS (n=51)	p VALUE
PALLOR	Present	5 (9.80%)	0	0.022*
	Absent	46 (90.20%)	51 (100%)	
PEDAL EDEMA	Present	32 (62.75%)	0	<0.001
	Absent	19 (37.25%)	51(100%)	
VULVAL EDEMA	Present	4 (7.84%)	0	0.041*
	Absent	47 (92.16)	51 (100%)	
BSUA	Present	37 (72.55%)	0	<0.001
	Absent	14 (27.45%)	51 (100%)	
ANEMIA	Present	9 (17.65%)	2 (3.92%)	0.040*
	Absent	42 (82.35%)	49 (96.08%)	
FGR	Present	9 (19.65%)	0	0.041*
	Absent	42 (82.35%)	51 (100%)	

Significant statistical results emerged when p value reached <0.05 and highly significant results emerged when p value reached <0.005.

Overall, the majority of patients (97 out of 102, 95.1%) did not exhibit pallor (within cases group 5 out of 51 patients showed presence of pallor (9.80%). However, none had pallor within control group. Hence, all patients with presence of pallor were

exclusively in Group 1. This suggests a potential association between pallor and the study groups warranting further investigation into its clinical significance.

The Pearson Chi-Square test result (*p value 0.022*) indicates a statistically significant association between pallor and the study groups at the 5% significance level. This suggests that the presence or absence of pallor is not evenly distributed between the study groups, implying that the intervention type may have an impact on pallor status.

32 out of 51 (62.75%) patients in Group 1 (cases) showed with presence of pedal edema while none in Group 2 had pedal edema. The Pearson Chi-Square test result (*p value <0.001*) indicates a statistically significant association between pedal edema and Group 1. This finding suggests that Group 1 is strongly associated with a higher prevalence of pedal edema compared to Group 2.

Presence of vulval edema is seen in 4 out of 51 (7.84%) patients. Analysis through Pearson Chi-Square test found a statistically significant connection between the vulval edema and Group 1 (*p value 0.041*). This suggests that the presence of vulval edema is not randomly distributed across the study groups. Specifically, all 4 cases of vulval edema were observed in Group 1, while none of the patients in Group 2 had vulval edema, indicating a potential effect of the intervention on the occurrence of vulval edema.

Our analysis reveals a statistically significant association between BSUA and the study group. Notably, all 37 cases out of 51 (72.55%) of BSUA were observed in Group 1, while none were found in Group 2, indicating a strong relationship between

the intervention and the presence of BSUA. Conversely, in the absence of BSUA, (14 cases) 27.45% of cases were in Group 1, and none were in Group 2. This suggests that the intervention may have a significant impact on BSUA occurrence.

The Pearson Chi-Square test establishes a highly significant association between Bed Side Urine Albumin test and the study group (Group 1) based on the obtained p value < 0.001 . This strong statistical significance suggests that the intervention plays a crucial role in influencing the presence of BSUA.

Distribution of anemia severity between the two groups were observed in our study, where patients in Group 1, 9 out 51 cases (17.65%) with 7 cases had moderate anemia and 2 cases had severe anemia, while in Group 2, 2 out of 51 cases (3.92%) had presence of moderate anemia, while the rest 42 cases in Group 1 (82.35%) and 49 cases in Group 2 (96.08%) showed no anemia.

The Pearson Chi-Square test yielded a p -value 0.040, indicating a statistically significant association between anemia severity and the study groups. This suggests that the distribution of anemia (mild, moderate, and severe) differs between the both groups, implying that certain interventions may be linked to variations in anemia prevalence.

The majority of cases 42 cases out of 51 (82.35%) in Group 1 and Group 2 did not exhibit FGR. However, FGR was present in 9 cases out of 102, with a higher occurrence only in Group 1, 9 out of 51 (19.65%). This distribution suggests a potential association between the study group (Group 1) and the incidence of FGR, which may warrant further investigation into the effectiveness of different interventions in managing fetal growth complications.

A statistical significant relationship emerges from the Pearson chi-square analysis that produces a *p value of 0.041*. This finding suggests that the occurrence of FGR may be influenced by the study groups emphasizing the importance of targeted clinical strategies to address fetal growth concerns effectively.

(Table -19) Table showing miRNA-210 in Group 1 (51 cases) in association with maternal, neonatal complications, duration of NICU stay and birth weight

(Mann Whiney U test was used)

IMMINENT ECLAMPSIA (8 Cases)					
Variable	Within Imminent Eclampsia Cases	Compared To Other Complications in Group 1	p Value	Neonatal Complications (Within Imminent Eclampsia Cases)	Duration Of NICU Stay (Within Imminent Eclampsia Cases)
miRNA-210 (Mean ± SD)	32.02 ± 9.2	22.68 ± 10.19	0.030*	Birth asphyxia (5 neonates)	5 days (2 neonate had prolonged stay up to 12 days) 4 days
Birth Weight	2.41 ± 0.37	2.74 ± 0.36	0.037*	Meconium aspiration syndrome (3 neonates)	
ANTEPARTUM ECLAMPSIA (4 cases)					
	Within Antepartum Eclampsia Cases	Compared To Other Complications in Group 1	P Value	Neonatal Complications (Within Antepartum Eclampsia Cases)	Duration Of NICU Stay (Within Antepartum Eclampsia Cases)
miRNA-210 (Mean±SD)	24.04 ± 11.97	25.24 ± 10.67	0.836	Birth asphyxia (2 neonates)	6 days 3 days
Birth Weight	2.69 ± 0.27	2.65 ± 0.40	0.857	Meconium aspiration syndrome (2 neonates)	

(Table 20) Table showing miRNA-210 in Group 1 (51 cases) in association with maternal, neonatal complications, duration of NICU stay and birth weight

HELLP SYNDROME (4 Cases)					
Variable	Within HELLP Syndrome Cases	Compared To Other Complications in Group 1	P Value	Neonatal Complications (Within HELLP Syndrome Cases)	Duration Of NICU Stay (Within HELLP Syndrome Cases)
miRNA-210 (Mean±SD)	34.97±15.81	23.62 ± 9.19	0.045*	Respiratory distress syndrome (4 neonates)	7 days
Birth weight	2.76 ± 0.24	2.64 ± 0.40	0.559		
PREMATURE RUPTURE OF MEMBRANES (4 Cases)					
Variable	Within PROM Cases	Compared To Other Complications in Group 1	P Value	Neonatal Complications (Within PROM Cases)	Duration Of NICU Stay (Within PROM Cases)
miRNA-210 (Mean ± SD)	24.40 ± 7.06	25.19 ± 11.17	0.892	Hyperbilirubinemia (4 neonates)	7 days
Birth weight	2.74 ± 0.27	2.64 ± 0.40	0.654		
ABRUPTIO PLACENTA (2 cases)					
Variable	Within Abruption Placenta Cases	Compared To Other Complications in Group 1	Neonatal Complications (Within Abruption Placenta Cases)		Duration Of NICU Stay (Within Abruption Placenta Cases)
miRNA-210 (Mean ± SD)	24.04 ± 0.47	25.16 ± 11.01	Respiratory distress syndrome (2 neonates)		5 days
Birth weight	2.85 ± 0.21	2.64 ± 0.39			

(Table 21) Table showing miRNA-210 in Group 1 (51 cases) in association with maternal, neonatal complications, duration of NICU stay and birth weight

SEVERE OLIGOHYDRAMNIOS (2 Cases)			
Variable	Within Severe Oligohydramnios Cases	Neonatal Complications (Within Severe Oligohydramnios Cases)	Duration Of NICU Stay (Within Severe Oligohydramnios Cases)
miRNA-210 (Mean ± SD)	17.26 ± 6.83	Respiratory distress syndrome (2 neonates)	4 Days
Birth Weight	3 ± 0.14		
HYPOTHYROIDISM (3 cases)			
Variable	Within Hypothyroidism Cases	Neonatal Complications and Duration of Stay Within Hypothyroidism Cases	
miRNA-210 (Mean ± SD)	17.61 ± 4.53	No neonatal complications	
Birth Weight	2.5 ± 0.86		
Rh NEGATIVE PREGNANCY (2 cases)			
Variable	Within Rh Negative Pregnancy Cases	Neonatal Complications and Duration of Stay Within Rh negative pregnancy Cases	
miRNA-210 (Mean ± SD)	20.56 ± 2.61	No neonatal complications	
Birth Weight	2.85 ± 0.35		

Significant statistical results emerged when p value reached <0.05 and highly significant results emerged when p value reached <0.005 .

(Table 19, 20, 21) depicts miRNA-210 levels in Group 1 (cases) study population affecting maternal, neonatal complications, and duration of NICU stay.

Out of 51 cases studied in Group 1, maternal complications occurred in 31 cases (60.78%) of patients and NICU admission was necessary for 24 neonates (47.06%). During the course of study we observed imminent eclampsia among 8 patients (26%) and 5 neonates born to mothers with imminent eclampsia experienced birth asphyxia along with 3 neonates developing meconium aspiration syndrome.

Patients with imminent eclampsia and HELLP syndrome demonstrated elevated mean of miRNA-210 levels compared to patients with other maternal complications based on the results of our study, while patients with other complications displayed slightly lower miRNA-210 levels than those with imminent eclampsia cases. This approach enables to establish a link between elevated miRNA-210 levels trigger maternal along with neonatal complications.

The evaluation of miRNA-210 expression revealed imminent eclampsia patients had a mean level of 32.02 ± 9.2 whereas the mean miRNA-210 of imminent eclampsia with comparison to other maternal complications in Group 1 demonstrated a mean level of 22.68 ± 10.19 with statistical significance at p value 0.030. The mean birth weight of eight neonates in imminent eclampsia cases were 2.74 ± 0.36 (p value 0.037) and 8 of these neonates required NICU admission for additional management thus indicating imminent eclampsia demonstrates higher neonatal morbidity than other maternal complications. The data shows that high miRNA-210 levels can result

in abnormal maternal placental development which causes spiral artery reactivity retention and improper blood flow and oxygen deprivation in the fetus leading to hypoxia. High levels of miRNA-210 expression is also seen in HELLP syndrome with mean level of 34.97 ± 15.81 whereas the mean miRNA-210 of HELLP syndrome with comparison to other maternal complications in Group 1 demonstrated a mean level of 23.62 ± 9.19 with statistical significance at *p value 0.045*.

The presence of neonatal complications requiring NICU hospital stay with prolonged time was found only in women who were diagnosed with imminent eclampsia, antepartum eclampsia and HELLP syndrome while also having abruptio placenta and premature rupture of membranes along with severe oligohydramnios. Neonatal complications did not occur among neonates born from hypothyroid and Rh negative mothers.

Results demonstrate that increased miRNA-210 expression links directly to disease progression in both maternal and neonate.

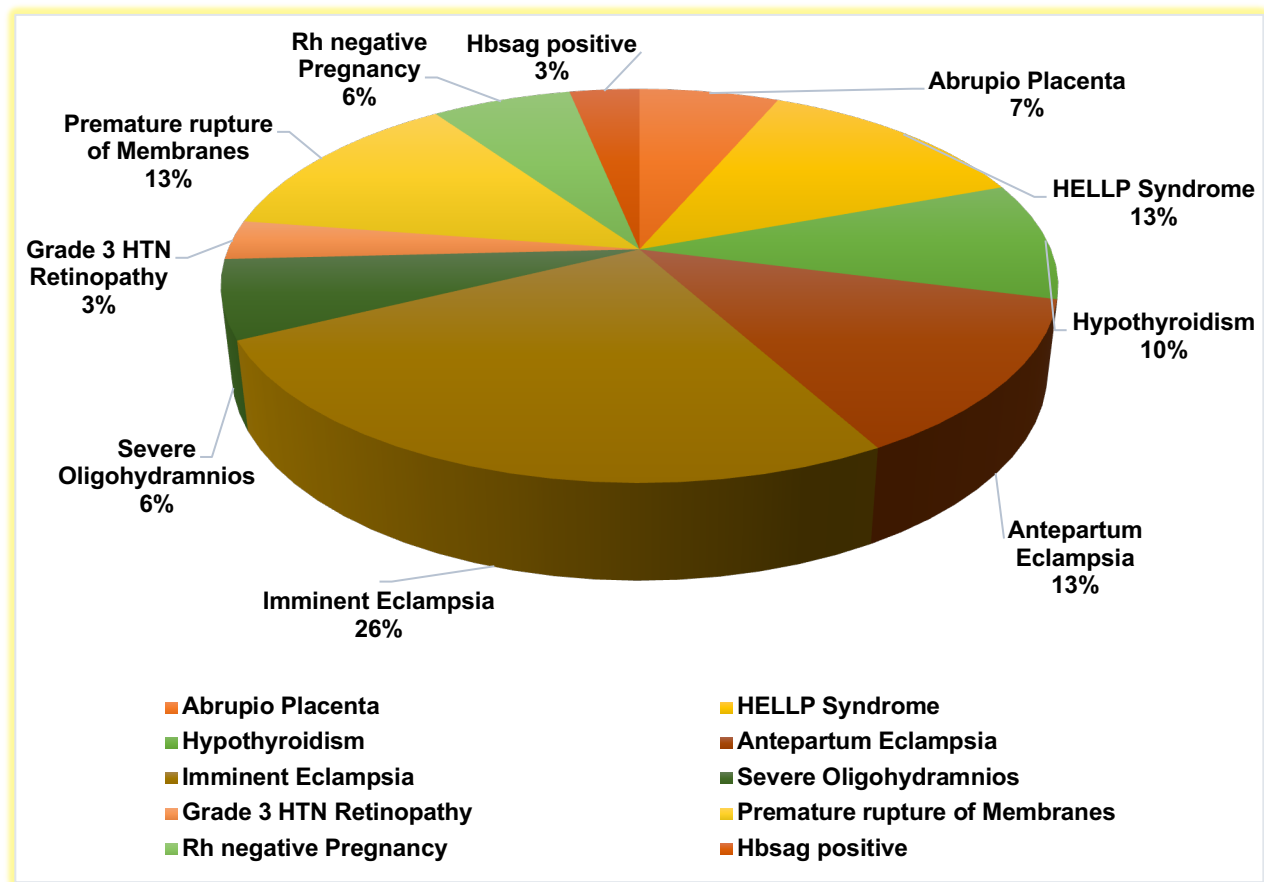
HELLP syndrome occurred in 4 pregnancies (13%) which led to respiratory distress syndrome as a birth complication for 4 newborns. The prevalence of antepartum eclampsia was 13% with birth asphyxia diagnosed in 2 neonates and meconium aspiration syndrome found in the other 2 neonates.

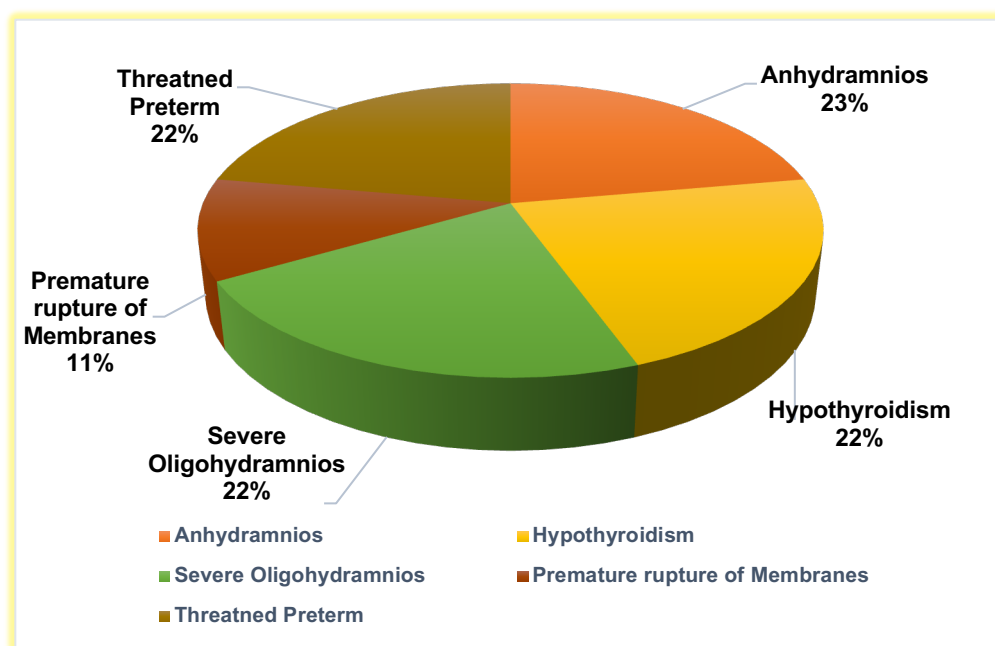
The study revealed 4 cases (13%) of premature rupture of membranes with five neonates to receive NICU admission because of hyperbilirubinemia. Abruptio placenta developed in 2 patients (7%) which resulted in respiratory distress in 2 newborns. Severe oligohydramnios seen in 2 patients (6%) while 2 neonates needed NICU admission.

Other maternal complications among Group 1 includes hypothyroidism seen in 3 patients (10%) and Rh negative pregnancy affected 2 patients (6%). The conditions of Hbsag positive status along with Grade 3 hypertensive retinopathy affected two patients (3%, 3%) in this group.

DISTRIBUTION OF MATERNAL COMPLICATIONS AMONG STUDY POPULATION:

(Figure - 18) Distribution of Maternal complications in Group I



(Figure - 19) Distribution of Maternal complications in Group II

The majority of cases (62 out of 102, 60.78%) had no additional complications, with a higher proportion (82.35%) were observed in intervention Group 2 (i.e., 42 out of 51 cases), while in Group 1, 20 cases of 51 (39.22%) had no complications. Total, 40 out of 102 (39.22%) patients had complications - divided among Group 1 with 31 cases (60.78%) and Group 2 with 9 cases (17.65%). Among specific complications, anhydramnios was reported in 2 cases, with a slightly higher occurrence in Group 2 (23%). Conditions such as HELLP syndrome (13%), abruptio placenta (7%) and several cases of imminent eclampsia (26%) were exclusively found in Group 1. Hypothyroidism, either alone or in combination with other conditions, was observed in a total of 5 cases (10% in Group 1, and 22% in Group 2), has with a mixed distribution across both intervention groups. Severe oligohydramnios and PROM was also seen in both categories, more prevalently seen in Group 1 (6%) and (13%), Group 2 (22%) and (11%) respectively. (22%) 2 cases of threatened preterm labor were recorded in Group 2, others, such as Rh-negative

pregnancy and Grade 3 Hypertensive Retinopathy, were solely found in Group 1. One pregnancy in Group 1 was complicated by HbsAg positive status. These findings highlight a varied distribution of complications across the two intervention study categories, suggesting a potential association between specific interventions and maternal-fetal outcomes.

DISTRIBUTION OF OUTCOME OF DELIVERY AMONG STUDY POPULATION:

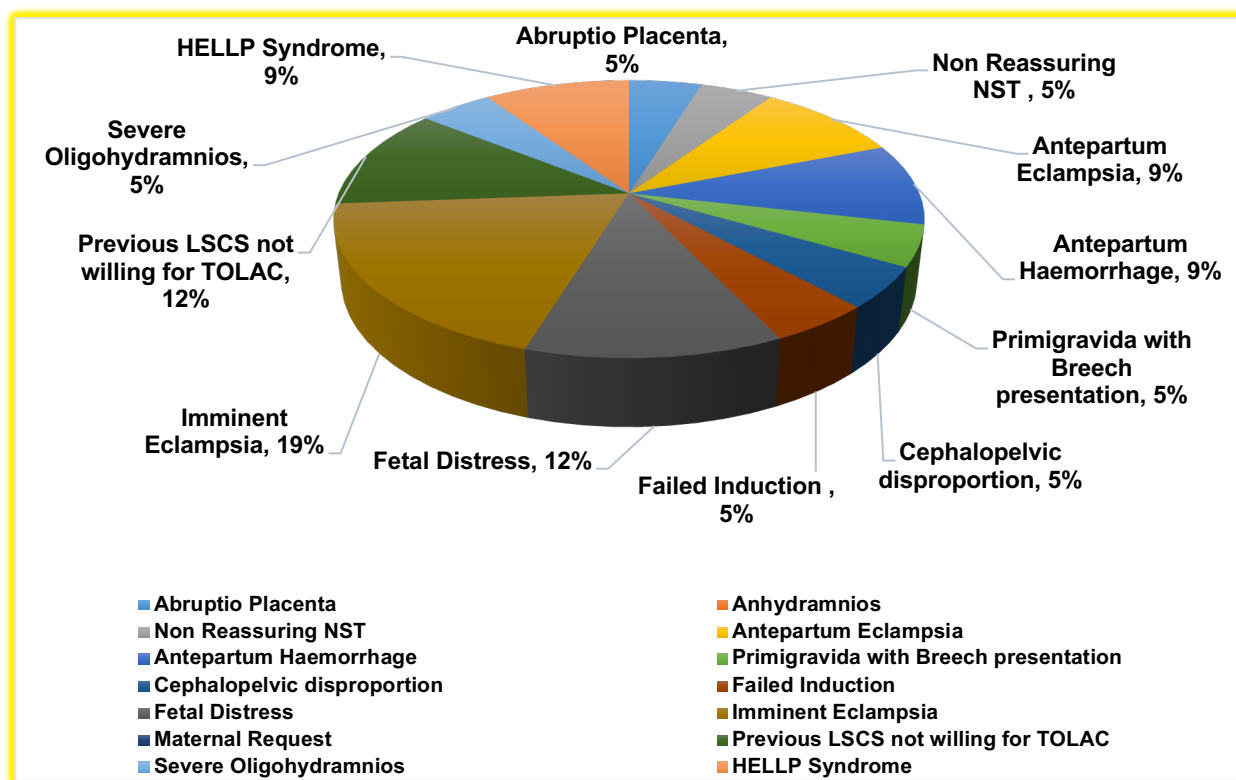
In Group 1, 42 cases out of 51 (82.35%) of deliveries were by Caesarean section, while 17.65% were delivered vaginally. In Group 2, the percentage of Caesarean section was lower (35 out of 51 cases) 68.63%, with a higher proportion of vaginal delivery (31.37%). Overall, across both intervention categories, 75.5% of deliveries were performed via LSCS, and 24.5% were Normal Vaginal Delivery. Elevated miRNA-210 levels during pregnancies of Group 1 led to maternal and neonatal complications. Addressing potential complications in both mother and fetus, caesarean section was chosen as the main delivery method for Group 1 patients. *(Table 19, 20, 21)*

The Pearson Chi-Square test was done and *p value is 0.107* which indicates no significance. This suggests that no significant impact was seen on whether the delivery outcome is by Caesarean section or vaginal delivery in the studied population.

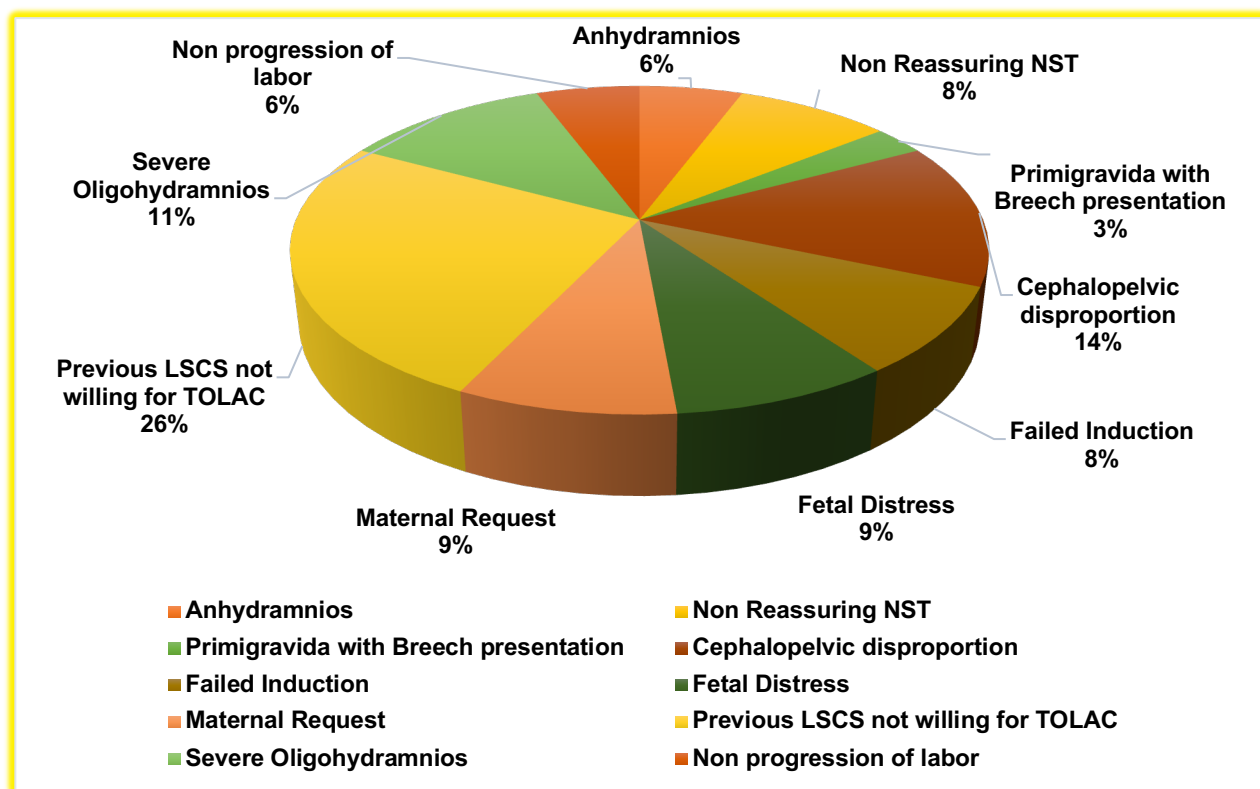
DISTRIBUTION OF INDICATIONS FOR CAESAREAN SECTION AMONG STUDY POPULATION:

The distribution of cases across various LSCS indications suggests variation in intervention categories, with diverse indications, such as imminent eclampsia (19%), previous LSCS not willing for TOLAC (12%), fetal distress, (12%), HELLP syndrome (9%), Antepartum Eclampsia (9%), Antepartum hemorrhage (9%), severe oligohydramnios (5%), Failed induction (5%), abruptio placenta (5%), and non reassuring NST (5%), majority of indication was previous caesarean section not willing for TOLAC (24%) is seen in Group 2. Previous LSCS not willing for TOLAC (26%), primigravida with breech presentation (5%), predominantly falls under Group 1, while in contrast, CPD (Cephalopelvic Disproportion) (14%), failed induction (9%), Anhydramnios (6%) show a higher proportion in Group 2.

(Figure - 20) Distribution Of Indications For Caesarean section in Group 1



(Figure - 21) Distribution Of Indications For Caesarean section in Group 2



The results highlight the diversity in clinical indications leading to LSCS and their corresponding management approaches.

Pearson chi-square test value showed *p value 0.395* which shows no statistically significant association between LSCS indications and the study groups. This suggests that the distribution of interventions across different LSCS indications is likely due to chance rather than a systematic pattern.

DISTRIBUTION OF SEX OF BABY AMONG STUDY POPULATION:

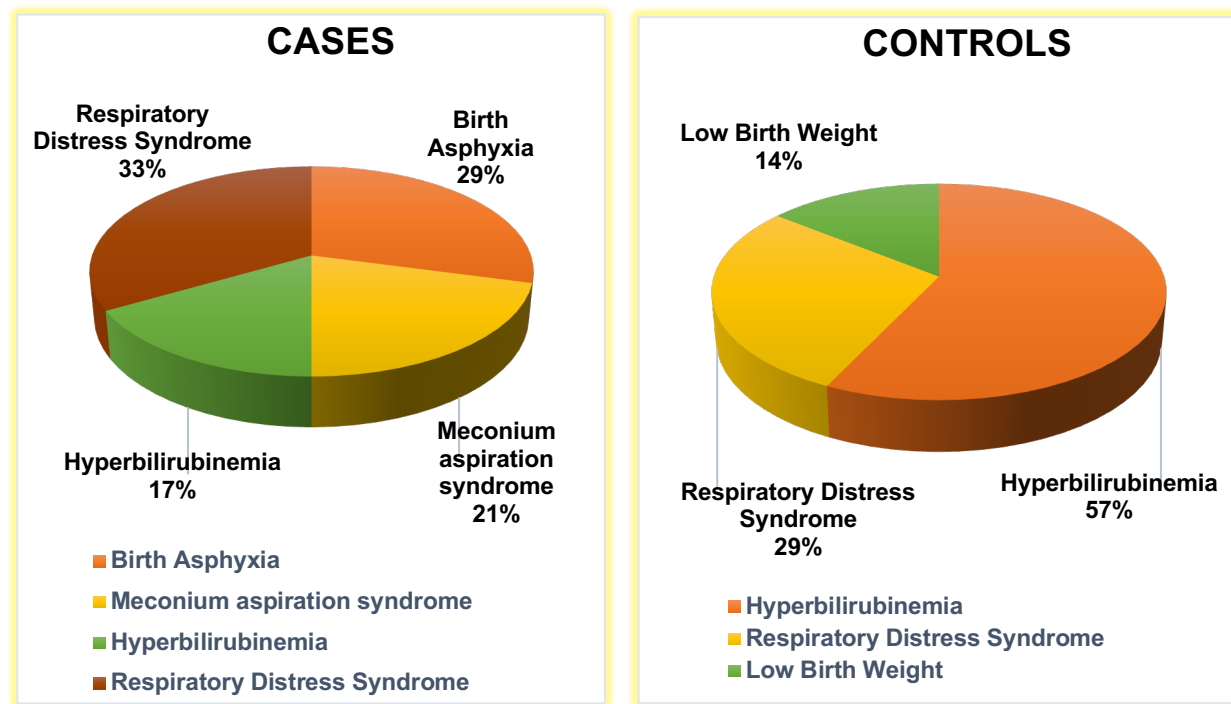
The analysis between the study groups and the sex of the baby shows an equal distribution. In each category, 45.09 % of the babies were female, and 54.91 % were male. This indicates that the category of intervention did not influence the sex distribution of the newborns, as the proportions remained identical across both groups.

Pearson Chi-Square value yielded *p value 1.000*. This indicates no statistically significant association between the study groups and the sex of the baby. The distribution of male and female babies is identical across both intervention groups, suggesting that sex is independent of the intervention category.

DISTRIBUTION OF NICU ADMISSION OF BABIES AMONG STUDY POPULATION:

When both study groups were analysed, total 31 babies out of 102 (30.4%) in which 24 Neonates in Group 1 were admitted in NICU was further management. Also, majority of NICU Admissions were in Group 1 due to, 7 babies out of 51 - (33%) are admitted mostly due to respiratory distress syndrome followed by birth asphyxia (29%), Meconium aspiration syndrome (21%) and hyperbilirubinemia (17%). One baby of low birth weight (14%) was predominately seen in Group 2.

(Figure - 22) Distribution of NICU Admission Of Babies Among Study Population



Pearson chi-square test showed p value <0.001 , indicating that the distribution of NICU admission across study groups does show a statistically significant relationship. The primary reason for NICU admission of Group 1 neonates was respiratory distress syndrome at a rate of 33%.

DISTRIBUTION OF DURATION OF STAY OF BABIES IN NICU AMONG STUDY POPULATION:

Most of the babies (71 out of 102, or 69.61%) had no NICU admission. The remaining cases had varying durations, with longer stays (e.g., 7, 8, 10 and 12 days) showing a relatively lower frequency. The proportion of cases across the study groups does not exhibit a clear trend, suggesting that duration of stay is relatively not evenly distributed. Majority of Group 1 neonates had prolonged stay in NICU upto 10-12 days.

Results of the Chi square analysis revealed a *p value of 0.045* indicates the existence of a significant relationship between NICU hospital stay duration and study groups. The findings suggest that the length of stay in the NICU is significantly influenced by the type of intervention received. (*Table 15, 16, 17*)

(Table- 22) Table showing miRNA-210 in study groups

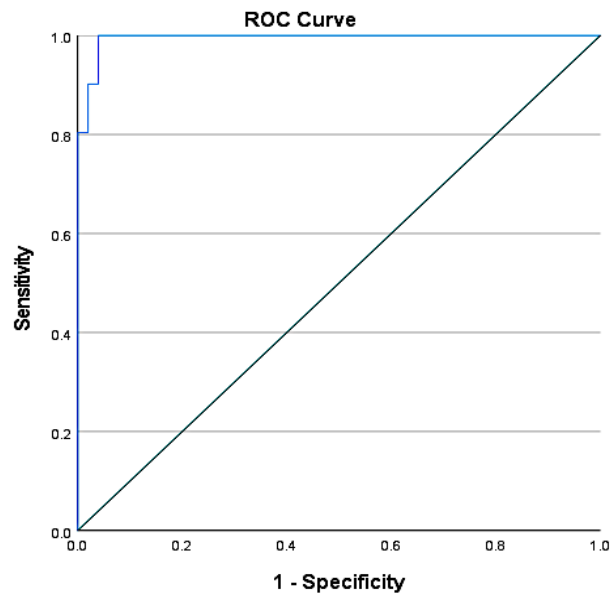
Study Groups											
with pre-eclampsia (cases n =51)						without pre-eclampsia (controls n =51)					
Item	Mean	SD	Median	Min.	Max	Mean	SD	Median	Min.	Max.	p Value
miRNA-210 (fold) (2^{-ΔΔCt})	25.41	10.13	23.66	10.10	53.24	2.05	3.35	0.65	0.0003	16.51	<0.001

**Mann Whiney U test was used.*

Above table (*Table-22*) presents a statistical comparison between two study groups, highlighting significant physiological differences. The expression of miRNA-210 is

markedly higher in Group 1 with Mean±SD (25.42 ± 10.14) compared to Group 2 Mean±SD (2.05 ± 3.35), suggesting a potential link with the intervention.

(Figure-23) showing ROC Curve of miRNA-210 in evaluation of PE

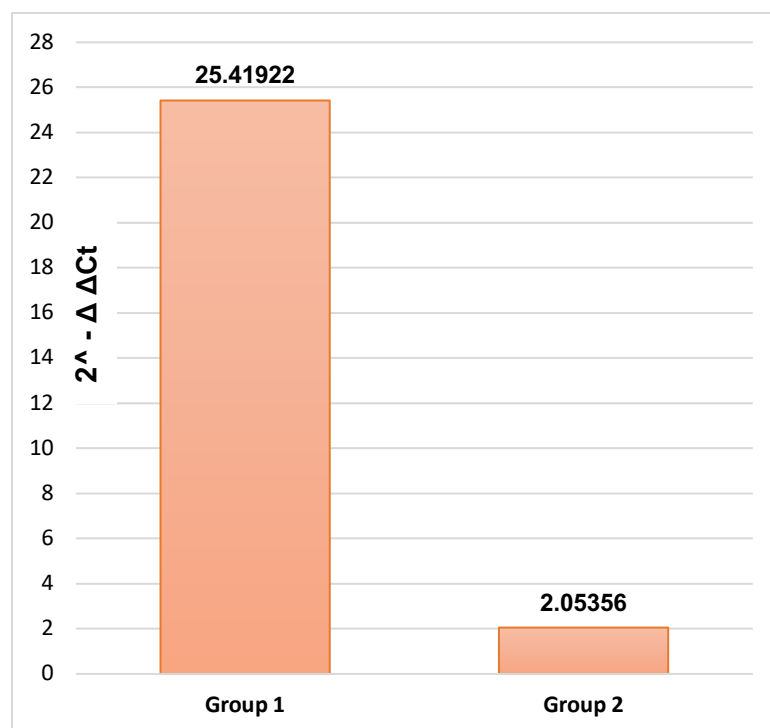


Area Under the Curve				
Test Result Variable(s): miRNA210 2 ^Δ - DDCα				
Asymptotic 95% Confidence Interval				
Area	Std. Error ^a	Asymptotic Sig. ^b	Lower Bound	Upper Bound
.994	.005	.000	.985	1.000

ROC analysis evaluated the diagnostic efficacy of miRNA-210 in identifying the cases of preeclampsia. The analysis showed a significant Area Under Curve (AUC) result of 0.9942 (*Figure 23*), which demonstrated a 95% confidence interval ranging from 0.985 to 1.0. At a cutoff value of 9.63 -fold change, the serum miRNA-210

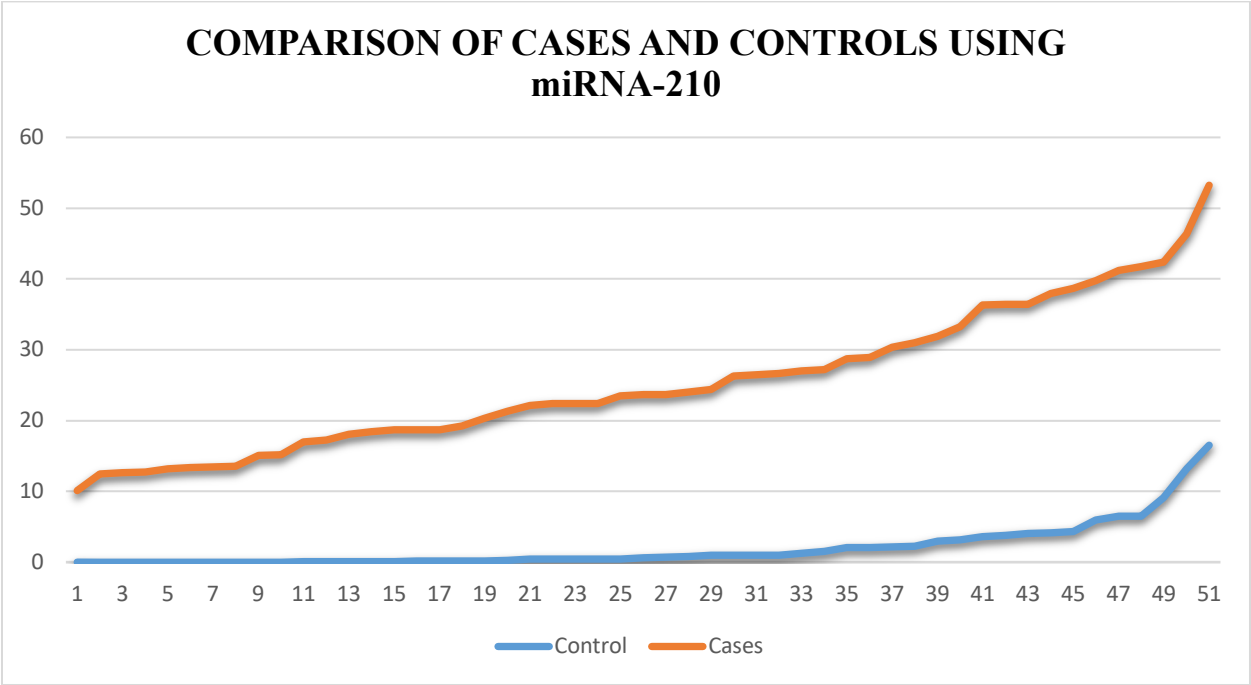
levels shows 100% sensitivity along with 96.1% specificity at while PPV and NPV values were 96.2% and 100%, respectively, and *p value* was observed as < 0.001 .

(Figure-24) miRNA - 210 in both study groups



Analysis through the bar graph indicates that Group 1 (cases) patients demonstrate a 25.41-fold increase in miRNA levels when compared to Group 2 (controls) patients at 2.05-fold. (Figure 24)

(Figure - 25) Line diagram showing comparison of miRNA-210 in study groups



The results demonstrate that miRNA -210 presents higher expression levels in pre-eclamptic patients when compared to normotensive healthy women. *(Figure 25)*

DISCUSSION

miRNA-210 ranks as one of several miRNAs that show greater expression levels in early to mid-gestation preeclamptic placenta and maternal plasma samples. Discovering the molecular pathways of miRNA-210 activity may lead to enhanced knowledge of PE pathophysiology with the discovery of emerging therapeutic targets.

The aim of our study is to evaluate the potential of miRNA-210 as a prognostic biomarker for pre-eclampsia by comparing its expression levels between pre-eclamptic cases and normotensive controls and by correlating these levels with clinical, biochemical, and fetal growth parameters.

In addition, the study examines the impact of these molecular changes on fetal development by assessing differences in head and abdominal circumferences, ultrasound doppler study and birth weight. The significance of this study lies in its potential to transform the early diagnosis and management of pre-eclampsia, a condition that poses substantial risks to both maternal and neonatal health. By identifying a non-invasive biomarker that reliably differentiates high-risk pregnancies, the study could enable clinicians to intervene earlier, thereby reducing the severity of complications and improving outcomes. The integration of detailed molecular profiling with comprehensive clinical assessments underscores the study's innovative approach and its capacity to offer a more proper understanding of the pathophysiological mechanisms underlying pre-eclampsia. Ultimately, the study aims to contribute to the development of personalized antenatal care strategies, where early risk stratification based on miRNA-210 expression could guide tailored interventions, enhance patient monitoring, and potentially decrease the rates of emergency cesarean sections and other adverse outcomes. This pioneering research

not only advances scientific knowledge in the field of obstetrics but also has important implications for public health by paving the way for improved screening protocols and targeted therapies in the management of pre-eclampsia.

A total of 102 consenting patients were taken into the study. Out of 102 patients, 51 patients were taken as cases and rest 51 are taken as controls. Majority of the study population (59.8%) belonged to the age group of 20-24 years, 24 patients (23.52%) belonged to 24-28 years, while 12.74% were in the age group of 28-32 years, and 4 (3.92%) in the age group of 31-36 years. The mean age of our study population in Group 1 was 24.55 ± 4.42 and Group 2 was 23.75 ± 3.70 years. A younger cohort, as observed in our study, may display different biomolecular profiles compared with older cohorts. Although our study did not directly correlate age (*p value 0.701*, $r=0.487$) with miRNA-210 levels, previous research has indicated that maternal age can influence gene expression profiles in the placenta. For instance, Lauren Anton et al. [85] found that even after adjusting for age, miRNA-210 levels remained a significant predictor of hypertensive disorders in pregnancy. Moreover, the age profile in our cohort is consistent with other studies conducted in similar geographical regions; Yousra M. Mammdoh et al. [78] also reported a predominantly young study population when assessing plasma miRNA-210 levels among at-risk women.

The findings from our study align with Jean-Ju Sheen et al [88] who discovered that severe morbidities primarily affect women in either the younger (<25 years) or older (>45 years) age categories. Risk of severe complications in pre-eclampsia patients followed a "U" pattern where the highest rates occurred among women between 18 to 24 years old and 40 to 54 years old. The lowest risks for abruption and acute renal failure and acute heart failure as well as pulmonary edema and stroke were observed

among women aged 15 to 24 years while these risks escalated as maternal age increased.

The study conducted by Teklit Grum et. al ^[89] revealed that the risk probability for pre-eclampsia among primigravida women exceeded that of multigravida women by a factor of 2.68. Our study demonstrates this trend because 58.82% of patients were primigravida.

Pallor was seen exclusively in Group 1 (9.80%) and *p* value 0.022, indicating a possible association between pallor and study groups. Elevated miRNA-210 levels are associated with clinical signs of poor perfusion and tissue hypoxia, which can manifest as pallor. Pooneh Nikuei et al. have discussed how hypoxia-induced miRNAs, particularly miRNA-210, rise in response to low oxygen tension, leading to clinical manifestations such as pallor ^[82].

In study done by Lionel Carbillon et al. ^[90] stated that during pre-eclampsia there is an observed connection between edema occurrences and reduced serum plasma ranges, which is significantly seen in our study with 32 patients in Group 1 (62.75%) had pedal edema with *p* value is <0.001 , serum protein (6.27 ± 0.73 vs. 6.043 ± 0.48) with *p* value 0.009 and serum albumin (3.04 ± 0.45 vs. 3.57 ± 0.56) *p* value < 0.001 . Thus, highlighting possible association between pedal edema, deranged serum and protein and albumin levels and study groups.

The exclusive clustering of BSUA {37 cases (72.55%)} cases in Group 1 suggests that the biochemical derangements observed in these patients are closely linked with the pathophysiology of pre-eclampsia. Elevated BSUA, elevated TSB (0.61 ± 0.41 vs. 0.43 ± 0.18) with *p* value 0.008, elevated unconjugated bilirubin (0.39 ± 0.35 vs.

0.25 $\pm$ 0.14) with p value 0.009, elevated ALP (253 $\pm$ 92 vs. 160 $\pm$ 51.96) with significant p value $<$ 0.001. Suggesting a strong association between elevated parameters and study groups.

The elevated parameters may reflect underlying hepatic stress and hemolysis—conditions frequently associated with severe forms of pre-eclampsia. In comparison, studies such as those by Fetnat M. Tolba et al.^[79] have similarly demonstrated that severe pre-eclampsia is accompanied by significant alterations in liver function tests and associated biomarkers, including elevated levels of miRNA-210. Moreover, Lauren Anton et al.^[85] reported that increased miRNA-210 was a significant predictor of adverse biochemical changes, including alterations in bilirubin metabolism, thereby linking molecular alterations with clinical laboratory findings.

Among 102 patients, antenatal complications occurred in 39.22%. No maternal mortality was observed in our study. 17.65% in Group 2 with 9 cases whereas Group 1 had a higher rate of 60.78% with 31 cases. Specific complications such as HELLP syndrome, antepartum hemorrhage (APH), and imminent eclampsia were differentially distributed between the intervention categories. Notably, complications like HELLP syndrome, abruptio placenta, Grade 3 HTN retinopathy and imminent eclampsia were found exclusively in Group 1, while certain conditions such as threatened preterm labor seen only in Group 2. Comparatively, similar results seen in studies done by Bisma Khan et. al.^[91] their study establishes clear links between maternal and fetal outcomes and the risk factors that lead to preeclampsia. Both elevated systolic and diastolic measures have direct impacts on premature delivery rates and delivery methods. Moreover, the presence of complications like HELLP syndrome, abruptio placenta, Grade 3 HTN retinopathy exclusively in Group 1 reinforces the notion that certain pathological processes—

such as endothelial dysfunction, coagulopathy, and hepatic stress—are more prevalent in patients with elevated miRNA-210 expression. This aligns with the conclusions of Fetnat M. Tolba et al,^[79] who reported that severe pre-eclampsia cases exhibited a higher incidence of multi-organ involvement.

The research by Kritpol Pasokpuckdee et al.^[92] indicated that preeclampsia elevated the number of cesarean deliveries overall. The absence of preeclampsia resulted in decreased overall caesarean section rates by 6.9% without impacting the Robson classification distribution ratios. In our study we observed that Caesarean section was performed for 42 out of 51 (82.35%) births within Group 1 to prevent further maternal and neonatal complications, while Caesarean section made up 75.49% of all births.

Our study population contained a wide variety of caesarean section indications that included abruptio placentae and non-reassuring NST along with antepartum eclampsia and imminent eclampsia as well as cephalopelvic disproportion (CPD) and previous caesarean section not willing for TOLAC. The prevalence of previous LSCS not willing for TOLAC among patients was 12% in Group 1 and 26% in the Group 2. A higher percentage of women in Group 1 underwent caesarean section for Imminent eclampsia (19%), Fetal distress (12%), HELLP syndrome (9%) and antepartum eclampsia (9%) and abruptio placenta (5%) while Group 2 had more cases of CPD (14%) and anhydramnios (6%). The higher rates of indications manifesting as imminent eclampsia in Group 1 reflect the impact of severe maternal pathology on delivery decisions. Research by Leila Katz et. al^[93] showed that the total Cesarean section rate reached 68% with 249 patients (50%) undergoing elective procedures followed by 92 patients (18.4%) requiring intrapartum sections for preeclampsia. Their analysis focused on patients presenting with severe

preeclampsia and chronic fetal distress as well as breech presentation, CPD, nonreassuring fetal heart rate and macrosomia in combination with one or more previous Cesarean sections.

The occurrence of fetal growth restriction was observed primarily in Group 1 with a prevalence of 9 cases (19.65%) through statistical analysis that produced a *p value of 0.041* which points to a potential connection between groups. Pathological processes like placental insufficiency and maternal vascular vasoconstriction establish themselves through these results in Group 1 patients. Hedayanti Sirenden et. al ^[94] observed fetal complications at a rate of 41.7% within the severe preeclampsia group with a statistical significance of $p \text{ value} \leq 0.05$.

Study by Masaya Takahashi et al. ^[95] suggests that medical assessment of fetal growth restriction at preeclampsia onset serves to predict both maternal and newborn outcomes.

Among the 102 babies delivered, NICU admission was required for 31 cases, primarily with respiratory distress syndrome affecting 33% Group 1 neonates, followed by birth asphyxia affecting 29% while meconium aspiration syndrome affected 21% and 17% neonates admitted due to hyperbilirubinemia. The NICU admission rate was higher (47.06%) among the neonates in Group 1 than in Group 2.

All newborns survived throughout the study period. Also, our study showed *p value* (chi square test) was found to be statistically significant *p value* < 0.001 and *p value* < 0.45 indicating possible association between need for NICU admission , duration of NICU stay and the study groups.

Our study confirmed research conducted by Remita Yuli Kusumaningrum et. al^[96] which demonstrated pre-eclampsia generated statistical significance (p value <0.001) by affecting neonatal asphyxia incidence resulting from fetal hypoxia because of maternal vascular vasoconstriction.

ASSOCIATION BETWEEN miRNA-210 AND CLINICAL & BIOCHEMICAL PARAMETERS:

The field of biomarker research now utilizes circulating miRNAs as promising diagnostic indicators because these molecules persist at stable levels in circulating blood.

Various studies demonstrate miRNA-210 functions as a key regulator across multiple pathophysiological pathways including cancer and oxidative stress and apoptosis.^[58] There is decreased oxygen tension at the feto–maternal interface in PE pregnancies because trophoblasts reconstruct maternal blood vessels.^[97] A study by Mayor-Lynn et al.^[56] showed that miRNA-210 controls more than 100 gene expressions in patients with PE.

Our study analysis revealed that the levels of plasma miRNA-210 were notably higher among pregnant women who had PE compared to normotensive pregnant women, which is found to similar to the studies done by Jairajpuri et al.^[77] Fetnat M Tolba et. al^[79] Yousra M. Mammdoh et al.^[78]

The mean miRNA-210 level in our study Group 1 (cases) was [mean ± SD (25.41 ± 10.13)], while in Group 2 (controls) it was [mean ± SD (2.053 ± 3.35)]. This

significant difference, with a p value of <0.001 , indicates a strong association between elevated miRNA-210 and the presence of pre-eclampsia. The clear separation in mean values supports the hypothesis that miRNA-210 is a critical biomarker for distinguishing between pre-eclamptic and normotensive pregnancies. Such findings are reinforced by previous studies by, Deeba S. Jairajpuri et. al ^[77] reported significant fold changes in miRNA-210 expression between mild and severe pre-eclampsia, with fold changes of 10.43 and 19.20, respectively, when compared to controls. Similarly, Yousra M. Mammdoh et al ^[78] observed markedly elevated plasma miRNA-210 levels in women with pre-eclampsia (mean $\pm$ SE: 19.23 ± 6.95) compared to those without (4.29 ± 1.36 ; $P = 0.001$). Furthermore, Qian Li et al ^[83] reported that increased miRNA-210 expression in maternal serum could predict pre-eclampsia with high accuracy (AUC of 0.93), underscoring its diagnostic potential. The large difference in mean values in our study not only highlights the biological significance of miRNA-210 but also suggests its potential as an early prognostic marker, capable of identifying women at risk long before clinical manifestations appear.

According to Gunel et al. ^[98], the plasma miRNA-210 was significantly higher among preeclamptic pregnant women than those pregnant women who are normotensive from week 24-40 of gestation.

Adel et al.^[73] stated that miRNA-210 is significantly expressed in preeclamptic primigravida placentas/serum compared with those in normotensive primigravidas, which correlates with our study findings, majority (58.83%) of the study population were primigravidas.

Ghafari et al.^[71] conducted study by collecting plasma from 90 pregnant women of gestational ages between 26 to 40 weeks and then separated the study population into pre-eclamptic (48) and control healthy pregnancy (42) groups. Research showed that pregnant women with preeclampsia had elevated levels of miRNA-210, 155 and 494 compared to patients without pre-eclampsia.

With p value <0.05 , systolic, diastolic, mean arterial blood pressure, SGOT, SGPT, Proteinuria, ALP and miRNA- 210 were significantly raised in PE patients (Group 1) than Group 2.

In both the study groups, we found that there was no significant difference between gestational age, BMI, Hb% levels, platelets, PT, INR, serum urea and creatinine (with p value of 0.322, 0.089, 0.996, 0.743, 0.672, 0.44, 0.502, 0.344, 0.754 respectively). PTT was also observed to be statistically significant in our study with p value <0.001 , and it was found to be within normal range which is also observed with other studies done by Lei Han et. al.^[99] and B Namavar Jahromi et. al.^[100]

Renal damage occurs as a primary complication of PE. Diagnosis of PE currently requires proteinuria as a necessary diagnostic factor. Multiple studies provide evidence between proteinuria levels and maternal perinatal outcome.^[101] Our study also reported this relationship with p value <0.001 with proteinuria and serum uric acid.

Other studies align with the our current study findings, between preeclampsia cases and healthy pregnant women significant elevation of bilirubin and liver enzymes levels in blood serum due to liver cell hypoxia resulting in hepatocyte necrosis.^[102] This increase was occurred in the first 20 weeks of gestation and predicted severe

preeclampsia development in later pregnancy, also results in a higher chance of complications for mothers and fetus. ^[103]

miRNA-210 in our study showed a significant positive co-relation with gestational age, SBP, DBP, MAP, PT, Urea, SGOT, SGPT, serum protein, albumin uric acid and ALP with *p value* <0.001 . Non-significant negative correlation was found in our study between miRNA-210 and maternal age, BMI, platelets, PTT (*p value* 0.487, 0.720, 0.198, 0.55 respectively), which aligns with study done by Fetnat M. Tolba et. al ^[79]

Conversely, miRNA-210 showed negative correlations with BMI ($r = -0.036$), platelets ($r = -0.128$), PTT ($r = -0.190$) and pulsatility index of MCA doppler ($r = -0.272$). These findings indicate that as miRNA-210 levels increase, the severity of hypertension and metabolic disturbances intensifies, while markers of fetal growth decline. Comparable evidence has been presented in previous research; for example, Lauren Anton et. al ^[85] reported that each incremental increase in miRNA-210 was associated with a 2.7-fold increase in the risk for hypertensive disorders. Similarly, Michal A. Elovitz et. al ^[86] found that elevated miRNA-210 levels increased the odds of developing pre-eclampsia by over fivefold, with significant correlations to adverse biochemical parameters. The robust positive correlations with blood pressure parameters, biochemical parameters suggest that miRNA-210 plays a central role in the pathogenesis of vascular dysfunction in pre-eclampsia. Furthermore, the inverse relationship with fetal growth parameters supports the notion that elevated miRNA-210 may impede trophoblast invasion and placental development, leading to growth restriction. Such comprehensive correlation analyses provide strong evidence for the utility of miRNA-210 as a multifaceted prognostic biomarker. The integration of these molecular and clinical correlations

further highlights the potential for miRNA-210 to serve as a central node linking maternal systemic alterations to fetal outcomes. This detailed correlation pattern reinforces the clinical relevance of monitoring miRNA-210 levels in pregnant women at risk for pre-eclampsia.

ROC analysis was performed for the diagnostic accuracy of miRNA-210 in preeclampsia. The AUC obtained was highly significant at 0.994, and the 95% confidence interval ranged from 0.985 to 1.0. At a cut off of 9.63-fold change, the serum miRNA-210 showed a sensitivity of 100% and a specificity of 96% with the PPV and NPV being 100% and 96%, respectively. Similar results were also observed in studies done by Lu Gan et al.^[81], and the ROC curve result was (AUC was 0.750 with 95% CI), Fetnat M. Tolba et.al^[79] ROC curve result was (AUC was 0.933 with 95% CI), Yousra M. Mammdoh et. al^[78] ROC curve result was (AUC of 0.852 with 95% CI) respectively. The high sensitivity and specificity associated with miRNA-210, as observed in meta-analyses done by Mehdi Koushki et. al^[70] and case-control studies done by Lauren Anton et. al^[81] and Michal A. Elovitz et. al^[86] further validate its role in the early detection and management of pre-eclampsia.

Multiple studies have confirmed the direct connection between PE development and modifications in tissue-specific and circulating miRNA expression patterns. Research shows miRNA-210 to be one of the prominent microRNAs associated with PE despite being known for its hypoxic response properties.

SUMMARY

- ⇒ Majority of the study population (59.8%) belonged to the age group of 20-24 years. The mean age of our study population in Group 1 was 24.55 ± 4.42 and Group 2 was 23.75 ± 3.70 years. This distribution indicates that our study primarily involved younger individuals.

- ⇒ The weight distribution of the study participants shows that the highest proportion of individuals (36.27%) had a weight between 65-70 kg.

- ⇒ Systolic blood pressure in Group 1 mean was 155.69 ± 15.27 mmHg, while in Group 2 it was 114.71 ± 7.03 mmHg.

- ⇒ Diastolic blood pressure in Group 1 mean measured 98.82 ± 8.64 mmHg versus 72.75 ± 6.03 mmHg in Group 2.

- ⇒ Mean arterial pressure in Group 1 was 117.80 ± 9.79 mmHg, compared to 86.57 ± 4.67 mmHg in Group 2.

- ⇒ Mann–Whitney U tests revealed highly significant differences in miRNA-210 (p value < 0.001), blood pressure parameters (p value < 0.001), uric acid (p value < 0.001), ALP (p value < 0.001), and serum albumin (p value < 0.001), PTT (p value < 0.001) serum protein (p value < 0.001), SGOT and SGPT (p value 0.041 and 0.032), as well as in fetal growth parameters (significant p-values for abdominal circumference, head circumference, and birth weight).

- ⇒ Chi-square tests showed significant associations for pallor (p value 0.022), pedal edema (p value < 0.001), vulval edema (p value 0.041), BSUA (p value < 0.001), anemia (p value 0.040), and fetal growth restriction (p value 0.041).
- ⇒ Correlation analysis demonstrated strong positive correlations between miRNA-210 and systolic blood pressure ($r = 0.723$), diastolic blood pressure ($r = 0.739$), mean arterial pressure ($r = 0.757$), uric acid ($r = 0.532$), and ALP ($r = 0.460$); serum protein ($r = 0.674$), serum albumin ($r = 0.328$), SGOT and SGPT ($r = 0.620$ and 0.650) while negative correlations were observed with BMI (-0.036), platelets (-0.128), PTT ($r = -0.190$), pulsatility index of MCA doppler ($r = -0.272$).
- ⇒ In terms of delivery outcomes, 82.35% of Category 1 deliveries were via LSCS compared to 68.62% in Category 2, while normal vaginal delivery (NVD) occurred in 17.64% of Category 1 and 31.37% of Category 2.
- ⇒ The miRNA-210 level in Group 1 (cases) was 25.42 ± 10.14 compared to mean in 2.05 ± 3.35 in Group 2 (controls).
- ⇒ AUC obtained was highly significant at 0.994, and the 95% confidence interval ranged from 0.985 to 1.0. At cut off 9.63 fold change miRNA-210 showed a sensitivity of 100% and a specificity of 96% with the PPV and NPV being 100% and 96%, respectively.
- ⇒ The clear difference in mean miRNA-210 levels between cases and controls underscores the association of elevated miRNA-210 with pre-eclampsia.

CONCLUSION

This study provides a comprehensive insight into the potential of miRNA-210 as a prognostic biomarker for pre-eclampsia by integrating detailed clinical, biochemical, and fetal growth parameters from two distinct intervention groups. The findings clearly demonstrate that Group 1, representing pre-eclamptic cases, exhibits significantly elevated miRNA-210 levels [mean $\pm$ SD (25.42 ± 10.14)] compared to Group 2 (controls) with levels of [mean $\pm$ SD (2.05 ± 3.35)], emphasizing a distinct molecular difference that is reflective of the pathological processes underlies pre-eclampsia.

Our study results provide compelling evidence that miRNA-210 holds promise as an early, non-invasive biomarker that could potentially be integrated into routine prenatal screening protocols to identify high-risk pregnancies. By enabling earlier diagnosis and intervention, the implementation of miRNA-210 measurement could transform clinical management strategies for pre-eclampsia, ultimately leading to improved maternal and neonatal outcomes. The integration of detailed molecular profiling with comprehensive clinical assessment offers a pathway toward personalized care in obstetrics, emphasizing the importance of early risk stratification in preventing the serious complications associated with pre-eclampsia. Results from our study enhance understanding about the fundamental molecular mechanisms responsible for pre-eclampsia and also facilitate for future research aimed at refining diagnostic criteria and exploring targeted therapeutic interventions that may mitigate the adverse outcomes associated with this condition.

LIMITATIONS

- ⇒ Though the study considered miRNA-210 gene alone, there are several other genes as well that can exhibit upregulation in pre-eclampsia and were not addressed in our study. Future research may consider a broader array of genetic markers to achieve a better insight.
- ⇒ The study was carried out at a single health care center which limits the variability of clinical practices and patient demographics. A multi-center study involving different geographic locations and healthcare facilities may provide a more comprehensive view.
- ⇒ With only 102 participants, the study sample might not accurately reflect the range of demographic traits and genetic origins found in the broader population. The findings would be more established and broadly applicable with a larger sample size.

BIBLIOGRAPHY

1. World Health Organization. WHO recommendations for prevention and treatment of pre-eclampsia and eclampsia. Geneva, Switzerland: World Health Organization; 2011. doi: 119627/WHO_RHR_14.17.
2. Burton GJ, Redman CW, Roberts JM, Moffett A. Pre-eclampsia: pathophysiology and clinical implications. *Bmj*. 2019 Jul 15;366. doi: 10.1136/bmj.l2381.
3. Zhao G, Zhou X, Chen S, Miao H, Fan H, Wang Z, Hu Y, Hou Y. Differential expression of microRNAs in decidua-derived mesenchymal stem cells from patients with pre-eclampsia. *Journal of Biomedical Science*. 2014 Dec;21:1-2. doi: 10.1186/s12929-014-0081-3.
4. Jaszczuk I, Koczkodaj D, Kondracka A, Kwaśniewska A, Winkler I, Filip A. The role of miRNA-210 in pre-eclampsia development. *Annals of medicine*. 2022 Dec 31;54(1):1350-6. doi: 10.1080/07853890.2022.2071459.
5. Park MH, Galan HL, Arroyo JA. Effect of hypoxia on endothelial nitric oxide synthase, NO production, intracellular survival signaling (p-ERK1/2 and p-AKT) and apoptosis in human term trophoblast. *American Journal of Reproductive Immunology*. 2011 Apr;65(4):407-14. doi: 10.1111/j.1600-0897.2010.00886.x.
6. Ramos Filho FL, Antunes CM. Hypertensive disorders: prevalence, perinatal outcomes and cesarean section rates in pregnant women hospitalized for delivery. *Revista Brasileira de Ginecologia e Obstetrícia*. 2020 Nov;42(11):690-6. doi: 10.1055/s-0040-1714134.
7. Saleem S, McClure EM, Goudar SS, Patel A, Esamai F, Garces A, Chomba E, Althabe F, Moore J, Kodkany B, Pasha O. A prospective study of maternal,

- fetal and neonatal deaths in low-and middle-income countries. *Bulletin of the World Health Organization*. 2014 Jun 5;92:605-12. doi: 10.2471/BLT.13.127464.
8. Zhou A, Xiong C, Hu R, Zhang Y, Bassig BA, Triche E, et al. Pre-Pregnancy BMI, Gestational Weight Gain, and the Risk of Hypertensive Disorders of Pregnancy: A Cohort Study in Wuhan, China. Rosenfeld CS, editor. *PLOS ONE*. 2015 Aug 25;10(8): e0136291. doi: 10.1371/journal.pone.0136291.
 9. Kuklina EV, Ayala C, Callaghan WM. Hypertensive disorders and severe obstetric morbidity in the United States. *Obstet Gynecol*. 2009;113:1299–1306. doi: 10.1097/AOG.0b013e3181a45b25.
 10. Poon LC, Shennan A, Hyett JA, Kapur A, Hadar E, Divakar H, McAuliffe F, da Silva Costa F, von Dadelszen P, McIntyre HD, Kihara AB. The International Federation of Gynecology and Obstetrics (FIGO) initiative on preeclampsia (PE): a pragmatic guide for first trimester screening and prevention. *International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics*. 2019 May;145(Suppl 1):1. doi: 10.1002/ijgo.12802.
 11. Tranquilli A, Dekker G, Magee L, Roberts J, Sibai BM, Steyn W, Zeeman GG, Brown MA. The classification, diagnosis and management of the hypertensive disorders of pregnancy: a revised statement from the ISSHP. *Pregnancy Hypertension: An International Journal of Women's Cardiovascular Health*. 2014 Apr 1;4(2):97-104. doi: 10.1016/j.preghy.2014.02.001.
 12. Magee LA, Pels A, Helewa M, Rey E, von Dadelszen P. Diagnosis, evaluation, and management of the hypertensive disorders of pregnancy. *Pregnancy Hypertension: An International Journal of Women's Cardiovascular Health*. 2014 Apr 1;4(2):105-45. doi: 10.1016/j.preghy.2014.01.003.

13. Lowe SA, Bowyer L, Lust K, McMahon LP, Morton M, North RA, Paech M, Said JM. SOMANZ guidelines for the management of hypertensive disorders of pregnancy 2014. Australian and New Zealand Journal of Obstetrics and Gynaecology. 2015 Oct;55(5):e1-29. doi: 1111/ajo.12399.
14. Brown MA, Magee LA, Kenny LC, Karumanchi SA, McCarthy FP, Saito S, Hall DR, Warren CE, Adoyi G, Ishaku S. Hypertensive disorders of pregnancy: ISSHP classification, diagnosis, and management recommendations for international practice. Hypertension. 2018 Jul;72(1):24-43. doi: 10.1161/hypertensionaha.117.10803.
15. National Collaborating Centre for Women's and Children's Health (UK). Hypertension in pregnancy: the management of hypertensive disorders during pregnancy. doi: PMID: 22220321 Bookshelf ID: [NBK62652](#)
16. Hypertension in Pregnancy. Obstetrics & Gynecology. 2013 Nov;122(5):1122–31. doi: 10.1097/01.AOG.0000437382.03963.88.
17. Redman CW, Sargent IL. Latest advances in understanding preeclampsia. Science. 2005 Jun 10;308(5728):1592-4. doi: 10.1126/science.1111726.
18. Jim B, Karumanchi SA. Preeclampsia: pathogenesis, prevention, and long-term complications. In Seminars in nephrology 2017 Jul 1 (Vol. 37, No. 4, pp. 386-397). WB Saunders. doi: 10.1016/j.semnephrol.2017.05.011
19. Chaiworapongsa T, Chaemsathong P, Yeo L, Romero R. Pre-eclampsia part 1: current understanding of its pathophysiology. Nature Reviews Nephrology. 2014 Aug;10(8):466-80. doi: 10.1038/nrneph.2014.102.
20. Jena MK, Sharma NR, Petitt M, Maulik D, Nayak NR. Pathogenesis of preeclampsia and therapeutic approaches targeting the placenta. Biomolecules. 2020 Jun 24;10(6):953. doi: 10.3390/biom10060953.

- 21.Zhang J, Meikle S, Trumble A. Severe maternal morbidity associated with hypertensive disorders in pregnancy in the United States. *Hypertension in pregnancy*. 2003 Jan 1;22(2):203-12. doi: 10.1081/PRG-120021066.
- 22.Chesley LC, Anitto JE, Cosgrove RA. The remote prognosis of eclamptic women: sixth periodic report. *American journal of obstetrics and gynecology*. 1976 Mar 1;124(5):446-59. doi: 10.1016/0002-9378(76)90168-X.
- 23.Brown MC, Best KE, Pearce MS, Waugh J, Robson SC, Bell R. Cardiovascular disease risk in women with pre-eclampsia: systematic review and meta-analysis. *European journal of epidemiology*. 2013 Jan;28:1-9. doi: 10.1007/s10654-013-9762-6.
- 24.Vikse BE, Irgens LM, Leivestad T, Skjærven R, Iversen BM. Preeclampsia and the risk of end-stage renal disease. *New England Journal of Medicine*. 2008 Aug 21;359(8):800-9. doi: 10.1056/NEJMoa0706790.
- 25.Carr DB, Newton KM, Utzschneider KM, Tong J, Gerchman F, Kahn SE, Easterling TR, Heckbert SR. Preeclampsia and risk of developing subsequent diabetes. *Hypertension in pregnancy*. 2009 Nov 1;28(4):435-47. doi: 10.3109/10641950802629675.
- 26.Yu CK, Khouri O, Onwudiwe N, Spiliopoulos Y, Nicolaides KH. Prediction of pre-eclampsia by uterine artery Doppler imaging: relationship to gestational age at delivery and small-for-gestational age. *Ultrasound in Obstetrics and Gynecology: The Official Journal of the International Society of Ultrasound in Obstetrics and Gynecology*. 2008 Mar;31(3):310-3. doi: 10.1002/uog.5252.
- 27.McDonald SD, Han Z, Walsh MW, Gerstein HC, Devereaux PJ. Kidney disease after preeclampsia: a systematic review and meta-analysis. *American journal of kidney diseases*. 2010 Jun 1;55(6):1026-39. doi: 10.1053/j.ajkd.2009.12.036.

28. Teramo KA, Hiilesmaa VK, Schwartz R, Clemons GK, Widness JA. Amniotic fluid and cord plasma erythropoietin levels in pregnancies complicated by preeclampsia, pregnancy-induced hypertension and chronic hypertension. doi: 10.1515/JPM.2004.045.
29. Aali BS, Malekpour R, Sedig F, Safa A. Comparison of maternal and cord blood nucleated red blood cell count between pre-eclamptic and healthy women. *Journal of Obstetrics and Gynaecology Research*. 2007 Jun;33(3):274-8. doi: 10.1111/j.1447-0756.2007.00523.x.
30. Ileakis JV, Reddy UM, Roberts JM. Preeclampsia—a pressing problem: an executive summary of a National Institute of Child Health and Human Development workshop. *Reproductive Sciences*. 2007 Sep;14(6):508-23. doi: 10.1177/1933719107306232.
31. Yücesoy G, Özkan S, Bodur H, Tan T, Çalışkan E, Vural B, Çorakçı A. Maternal and perinatal outcome in pregnancies complicated with hypertensive disorder of pregnancy: a seven year experience of a tertiary care center. *Archives of gynecology and obstetrics*. 2005 Nov;273:43-9. doi: 10.1007/s00404-005-0741-3.
32. Duley L. The global impact of pre-eclampsia and eclampsia. In *Seminars in perinatology* 2009 Jun 1 (Vol. 33, No. 3, pp. 130-137). WB Saunders. doi: 10.1053/j.semperi.2009.02.010.
33. Osmond C, Barker D. Fetal, infant, and childhood growth are predictors of coronary heart disease, diabetes, and hypertension in adult men and women. *Environmental health perspectives*. 2000 Jun;108(suppl 3):545-53. doi: 10.1289/ehp.00108s3545.
34. Chappell LC, Brocklehurst P, Green ME, Hunter R, Hardy P, Juszczak E, Linsell L, Chiocchia V, Greenland M, Placzek A, Townend J. Planned early delivery or expectant management for late preterm pre-eclampsia

- (PHOENIX): a randomised controlled trial. *The Lancet*. 2019 Sep 28;394(10204):1181-90. doi: 10.1016/S0140-6736(19)31963-4.
35. Phelps AJ, Holmgren C. Relationship between risk factor profile and prescription of low-dose aspirin for preeclampsia prevention. *Archives of gynecology and obstetrics*. 2023 Oct;308(4):1279-86. doi: 10.21203/rs.3.rs-1562224/v1.
 36. Visintin C, Mugglestone MA, Almerie MQ, Nherera LM, James D, Walkinshaw S. Management of hypertensive disorders during pregnancy: summary of NICE guidance. *Bmj*. 2010 Aug 25;341. doi: 10.1136/bmj.c2207.
 37. MacDonald TM, Walker SP, Hannan NJ, Tong S, Tu'uhevaha J. Clinical tools and biomarkers to predict preeclampsia. *EBioMedicine*. 2022 Jan 1;75. doi: 10.1016/j.ebiom.2021.103780.
 38. Poon LC, Kametas NA, Maiz N, Akolekar R, Nicolaides KH. First-trimester prediction of hypertensive disorders in pregnancy. *Hypertension*. 2009 May 1;53(5):812-8. doi: 10.1161/HYPERTENSIONAHA.108.127977.
 39. Laganà AS, Giordano D, Loddo S, Zoccali G, Vitale SG, Santamaria A, Buemi M, D'Anna R. Decreased Endothelial Progenitor Cells (EPCs) and increased Natural Killer (NK) cells in peripheral blood as possible early markers of preeclampsia: a case-control analysis. *Archives of gynecology and obstetrics*. 2017 Apr;295:867-72. doi: 10.1007/s00404-017-4296-x.
 40. Laganà AS, Vitale SG, Sapia F, Valenti G, Corrado F, Padula F, Rapisarda AM, D'Anna R. miRNA expression for early diagnosis of preeclampsia onset: hope or hype?. *The journal of maternal-fetal & neonatal medicine*. 2018 Mar 19;31(6):817-21. doi: 10.1080/14767058.2017.1296426.
 41. Feingold EA, Good PJ, Guyer MS, Kamholz S, Liefer L, Wetterstrand K, Collins FS, Gingeras TR, Kampa D, Sekinger EA, Cheng J. The ENCODE

- (ENCyclopedia of DNA elements) project. *Science*. 2004;306(5696):636-40. doi: 10.1126/science.1105136.
- 42.Amaral PP, Mattick JS. Noncoding RNA in development. *Mammalian genome*. 2008 Aug;19:454-92. doi: 10.1007/s00335-008-9136-7.
 - 43.Ponting CP, Oliver PL, Reik W. Evolution and functions of long noncoding RNAs. *Cell*. 2009 Feb 20;136(4):629-41. doi: 10.1016/j.cell.2009.02.006.
 - 44.Kaikkonen MU, Lam MT, Glass CK. Non-coding RNAs as regulators of gene expression and epigenetics. *Cardiovascular research*. 2011 Jun 1;90(3):430-40. doi: 10.1093/cvr/cvr097.
 - 45.Qi J, Wu B, Chen X, Wei W, Yao X. Diagnostic biomolecules and combination therapy for pre-eclampsia. *Reproductive Biology and Endocrinology*. 2022 Sep 6;20(1):136. doi: 10.1186/s12958-022-01003-3.
 - 46.Ratti M, Lampis A, Ghidini M, Salati M, Mirchev MB, Valeri N, Hahne JC. MicroRNAs (miRNAs) and long non-coding RNAs (lncRNAs) as new tools for cancer therapy: first steps from bench to bedside. *Targeted oncology*. 2020 Jun;15:261-78. doi: 10.1007/s11523-020-00717-x.
 - 47.Adams BD, Kasinski AL, Slack FJ. Aberrant regulation and function of microRNAs in cancer. *Current Biology*. 2014 Aug 18;24(16):R762-76. doi: 10.1016/j.cub.2014.06.043.
 - 48.Croce CM, Calin GA. miRNAs, cancer, and stem cell division. *Cell*. 2005 Jul 15;122(1):6-7. doi: 10.1016/j.cell.2005.06.036.
 - 49.MacFarlane LA. R Murphy P (2010). MicroRNA: Biogenesis, function and role in cancer. *Curr Genomics*;11(7):537-61. doi: 10.2174/138920210793175895.
 - 50.Gallo A. RNA editing enters the limelight in cancer. *Nature Medicine*. 2013 Feb;19(2):130-1. doi: 10.1038/nm.3072.

- 51.Mannion N, Arieti F, Gallo A, Keegan LP, O'Connell MA. New insights into the biological role of mammalian ADARs; the RNA editing proteins. *Biomolecules*. 2015 Sep 30;5(4):2338-62. doi: 10.3390/biom5042338.
- 52.Hornakova A, Kolkova Z, Holubekova V, Loderer D, Lasabova Z, Biringer K, Halasova E. Diagnostic potential of microRNAs as biomarkers in the detection of preeclampsia. *Genetic Testing and Molecular Biomarkers*. 2020 Jun 1;24(6):321-7. doi: 10.1089/gtmb.2019.0264.
- 53.Slezak-Prochazka I, Durmus S, Kroesen BJ, van den Berg A. MicroRNAs, macrocontrol: regulation of miRNA processing. *Rna*. 2010 Jun 1;16(6):1087-95. doi: 10.1261/rna.1804410.
- 54.Broughton JP, Lovci MT, Huang JL, Yeo GW, Pasquinelli AE. Pairing beyond the seed supports microRNA targeting specificity. *Molecular cell*. 2016 Oct 20;64(2):320-33. doi: 10.1016/j.molcel.2016.09.004.
- 55.Pineles BL, Romero R, Montenegro D, Tarca AL, Han YM, Kim YM, Draghici S, Espinoza J, Kusanovic JP, Mittal P, Hassan SS. Distinct subsets of microRNAs are expressed differentially in the human placentas of patients with preeclampsia. *American journal of obstetrics and gynecology*. 2007 Mar 1;196(3):261-e1. doi:10.1016/j.ajog.2007.01.008.
- 56.Mayor-Lynn K, Toloubeydokhti T, Cruz AC, Chegini N. Expression profile of microRNAs and mRNAs in human placentas from pregnancies complicated by preeclampsia and preterm labor. *Reproductive sciences*. 2011 Jan;18(1):46-56. doi: 10.1177/1933719110374115.
- 57.Enquobahrie DA, Abetew DF, Sorensen TK, Willoughby D, Chidambaram K, Williams MA. Placental microRNA expression in pregnancies complicated by preeclampsia. *American journal of obstetrics and gynecology*. 2011 Feb 1;204(2):178-e12. doi: 10.1016/j.ajog.2010.09.004.

- 58.Muralimanoharan S, Guo C, Myatt L, Maloyan A. Sexual dimorphism in miR-210 expression and mitochondrial dysfunction in the placenta with maternal obesity. *International journal of obesity*. 2015 Aug;39(8):1274-81. doi: 10.1038/ijo.2015.45.
- 59.Kopriva SE, Chiasson VL, Mitchell BM, Chatterjee P. TLR3-induced placental miR-210 down-regulates the STAT6/interleukin-4 pathway. *PloS one*. 2013 Jul 2;8(7):e67760. doi: 10.1371/journal.pone.0067760.
- 60.Chan YC, Banerjee J, Choi SY, Sen CK. miR-210: The master hypoxamir. *Microcirculation*. 2012 Apr;19(3):215-23. doi: 10.1111/j.1549-8719.2011.00154.x.
- 61.Zhang Y, Fei M, Xue G, Zhou Q, Jia Y, Li L, Xin H, Sun S. Elevated levels of hypoxia-inducible microRNA-210 in pre-eclampsia: new insights into molecular mechanisms for the disease. *Journal of cellular and molecular medicine*. 2012 Feb;16(2):249-59. doi: 10.1111/j.1582-4934.2011.01291.x
- 62.Luo R, Shao X, Xu P, Liu Y, Wang Y, Zhao Y, Liu M, Ji L, Li YX, Chang C, Qiao J. MicroRNA-210 contributes to preeclampsia by downregulating potassium channel modulatory factor 1. *Hypertension*. 2014 Oct;64(4):839-45. doi:10.1161/ HYPERTENSIONAHA.114.03530.
- 63.Muralimanoharan S, Maloyan A, Mele J, Guo C, Myatt LG, Myatt L. MIR-210 modulates mitochondrial respiration in placenta with preeclampsia. *Placenta*. 2012 Oct 1;33(10):816-23. doi: 10.1016/j.placenta.2012.07.002.
- 64.Lee DC, Romero R, Kim JS, Tarca AL, Montenegro D, Pineles BL, et al. miR-210 targets iron-sulfur cluster scaffold homologue in human trophoblast cell lines: siderosis of interstitial trophoblasts as a novel pathology of preterm preeclampsia and small-for-gestational-age pregnancies. *Am J Pathol* (2011) 179(2):590–602. doi:10.1016/j.ajpath.2011.04.035.

65. Zhu XM, Han T, Sargent IL, Yin GW, Yao YQ. Differential expression profile of microRNAs in human placentas from preeclamptic pregnancies vs normal pregnancies. *American journal of obstetrics and gynecology*. 2009 Jun 1;200(6):661-e1. doi:10.1016/j.ajog.2008.12.045.
66. Huang X, Le QT, Giaccia AJ. MiR-210—micromanager of the hypoxia pathway. *Trends in molecular medicine*. 2010 May 1;16(5):230-7. doi: 10.1016/j.molmed.2010.03.004.
67. Mutharasan RK, Nagpal V, Ichikawa Y, Ardehali H. microRNA-210 is upregulated in hypoxic cardiomyocytes through Akt-and p53-dependent pathways and exerts cytoprotective effects. *American Journal of Physiology-Heart and Circulatory Physiology*. 2011 Oct;301(4):H1519-30. doi:10.1152/ajpheart.01080.2010.
68. Ivan M, Huang X. miR-210: fine-tuning the hypoxic response. *Tumor Microenvironment and Cellular Stress: Signaling, Metabolism, Imaging, and Therapeutic Targets*. 2014:205-27. doi: 10.1007/978-1-4614-5915-6_10.
69. Youssef HM, Marei ES. Association of MicroRNA-210 and MicroRNA-155 with severity of preeclampsia. *Pregnancy Hypertension*. 2019 Jul 1;17:49-53. doi: 10.1016/j.preghy.2019.05.010.
70. Koushki M, Atan NA, Omid-Ardali H, Tavirani MR. Assessment of correlation between miR-210 expression and pre-eclampsia risk: a meta-analysis. *Reports of Biochemistry & Molecular Biology*. 2018 Oct;7(1):94. doi: PMID: 30324123 PMCID: [PMC6175589](https://pubmed.ncbi.nlm.nih.gov/30324123/).
71. Ghafari A, Lessan pezeshki M, Saffari M. P0069 MICRO RNA 155, 210, 494, 29B AND 34A EXPRESSION PROFILE IN PREECLAMPSIA AND NORMAL PREGNANCIES. *Nephrology Dialysis Transplantation*. 2020 Jun 1;35(Supplement_3):gfaa142-P0069. doi: 10.1093/ndt/gfaa142.P0069.

- 72.Hromadnikova I, Kotlabova K, Hympanova L, Krofta L. Gestational hypertension, preeclampsia and intrauterine growth restriction induce dysregulation of cardiovascular and cerebrovascular disease associated microRNAs in maternal whole peripheral blood. *Thrombosis research*. 2016 Jan 1;137:126-40. doi: 10.1016/j.thromres.2015.11.032.
- 73.Adel S, Mansour A, Louka M, Matboli M, Elmekkawi SF, Swelam N. Evaluation of MicroRNA-210 and Protein tyrosine phosphatase, non-receptor type 2 in Pre-eclampsia. *Gene*. 2017 Jan 5;596:105-9. doi: 10.1016/j.gene.2016.10.014.
- 74.Lawrie CH, Gal S, Dunlop HM, Pushkaran B, Liggins AP, Pulford K, Banham AH, Pezzella F, Boultonwood J, Wainscoat JS, Hatton CS. Detection of elevated levels of tumour-associated microRNAs in serum of patients with diffuse large B-cell lymphoma. *British journal of haematology*. 2008 Jun;141(5):672-5. doi: 10.1111/j.1365-2141.2008.07077.x.
- 75.Tomkiewicz J, Darmochwał-Kolarz DA. Biomarkers for early prediction and management of preeclampsia: a comprehensive review. *Medical Science Monitor: International Medical Journal of Experimental and Clinical Research*. 2024 May 23;30:e944104-1. doi: 10.12659/MSM.944104.
- 76.Morey R, Poling L, Srinivasan S, Martinez-King C, Anyikam A, Zhang-Rutledge K, To C, Hakim A, Mochizuki M, Verma K, Mason A. Discovery and verification of extracellular microRNA biomarkers for diagnostic and prognostic assessment of preeclampsia at triage. *Science Advances*. 2023 Dec 20;9(51):eadg7545. doi: 10.1126/sciadv.adg7545.
- 77.Jairajpuri DS, Malalla ZH, Sarray S, Mahmood N. Analysis of differential expression of hypoxia-inducible microRNA-210 gene targets in mild and severe preeclamptic patients. *Non-coding RNA Research*. 2021 Mar 1;6(1):51-7. doi: 10.1016/j.ncrna.2021.03.001.

- 78.Mammdoh YM, Omar H, Mohamed OA, Abbas AM, El-din LT. Predictive value of microRNA-210 in preeclampsia. *Journal of Current Medical Research and Practice*. 2023 Apr 1;8(2):74-8. doi: 10.4103/jcmrp.jcmrp_53_21.
- 79.Tolba F, Agha A, Rachwan M, Sakr B, Abdella M, Abdelrahman A. Evaluation of MicroRNA-210 (miR-210) as a diagnostic and prognostic biomarker in pre-eclampsia pregnancies. *Benha Medical Journal*. 2021 Apr 1;38(1):79-93. doi: 10.21608/bmfj.2020.120287.
- 80.Hornakova A, Kolkova Z, Holubekova V, Loderer D, Lasabova Z, Biringer K, Halasova E. Diagnostic potential of microRNAs as biomarkers in the detection of preeclampsia. *Genetic Testing and Molecular Biomarkers*. 2020 Jun 1;24(6):321-7. doi: 10.1089/gtmb.2019.0264.
- 81.Gan L, Liu Z, Wei M, Chen Y, Yang X, Chen L, Xiao X. MiR-210 and miR-155 as potential diagnostic markers for pre-eclampsia pregnancies. *Medicine*. 2017 Jul 1;96(28):e7515. doi: 10.1097/MD.00000000000007515.
- 82.Nikuei P, Davoodian N, Tahamtan I, Keshtkar AA. Predictive value of miR-210 as a novel biomarker for pre-eclampsia: a systematic review protocol. *BMJ open*. 2016 Sep 1;6(9):e011920. doi: 10.1136/bmjopen-2016-011920.
- 83.Li Q, Long A, Jiang L, Cai L, Xie LI, Gu JA, Chen X, Tan L. Quantification of preeclampsia-related microRNAs in maternal serum. *Biomedical reports*. 2015 Nov 1;3(6):792-6. doi: 10.3892/br.2015.524.
- 84.Ura B, Feriotto G, Monasta L, Bilel S, Zweyer M, Celeghini C. Potential role of circulating microRNAs as early markers of preeclampsia. *Taiwanese Journal of Obstetrics and Gynecology*. 2014 Jun 1;53(2):232-4. doi: 10.1016/j.tjog.2014.03.001.
- 85.Anton L, Olarerin-George AO, Schwartz N, Srinivas S, Bastek J, Hogenesch JB, Elovitz MA. miR-210 inhibits trophoblast invasion and is a serum

- biomarker for preeclampsia. *The American journal of pathology*. 2013 Nov 1;183(5):1437-45. doi: 10.1016/j.ajpath.2013.07.021.
- 86.Elovitz MA, Olarein-George A, Bastek J, Anton L, Schwartz N, Srinivas S, Hogenesh J. 83: MicroRNA 210 is associated and predicts the development of preeclampsia. *American Journal of Obstetrics & Gynecology*. 2012 Jan 1;206(1):S51-2. doi: 10.1016/j.ajog.2011.10.872.
- 87.Abalos E, Cuesta C, Grosso AL, Chou D, Say L. Global and regional estimates of preeclampsia and eclampsia: a systematic review. *European journal of obstetrics & gynecology and reproductive biology*. 2013 Sep 1;170(1):1-7. doi: 10.1016/j.ejogrb.2013.05.005.
- 88.Sheen JJ, Huang Y, Andrikopoulou M, Wright JD, Goffman D, D'Alton ME, Friedman AM. Maternal age and preeclampsia outcomes during delivery hospitalizations. *American journal of perinatology*. 2020 Jan;37(01):044-52. Doi: 10.1055/s-0039-1694794.
- 89.Grüm T, Seifu A, Abay M, Angsom T, Tsegay L. Determinants of preeclampsia/Eclampsia among women attending delivery Services in Selected Public Hospitals of Addis Ababa, Ethiopia: a case control study. *BMC pregnancy and childbirth*. 2017 Dec;17:1-7.doi: 10.1186/s12884-017-1507-1.
- 90.Carbillon L, Boujenah J. Edema associated with low plasma protein level and any gestational hypertension as warning signs of HELLP syndrome. *The Journal of Maternal-Fetal & Neonatal Medicine*. 2022 Dec 12;35(25):7395-8. doi:10.1080/14767058.2021.1949444.
- 91.Khan B, Yar RA, Khan Khakwani A, Karim S, Ali HA, Khakwani A, Karim S. Preeclampsia incidence and its maternal and neonatal outcomes with associated risk factors. *Cureus*. 2022 Nov 6;14(11). doi: 10.7759/cureus.31143.

- 92.Pasokpuckdee K, Boriboonhirunsarn D. Incidence of preeclampsia and cesarean section rate according to the Robson classification. *Cureus*. 2023 Dec 2;15(12). doi: 10.7759/cureus.49845.
- 93.Amorim MM, Katz L, Barros AS, Almeida TS, Souza AS, Faúndes A. Maternal outcomes according to mode of delivery in women with severe preeclampsia: a cohort study. *The Journal of Maternal-Fetal & Neonatal Medicine*. 2015 Apr 13;28(6):654-60. doi: 10.1016/j.preghy.2014.10.135.
- 94.Sirenden H, Sunarno I, Arsyad MA, Idris I. Birth weight, Apgar score, and fetal complications in mothers with severe preeclampsia. *Enfermeria clinica*. 2020 Mar 1;30:533-6. doi: 10.1016/j.enfcli.2019.07.154.
- 95.Takahashi M, Makino S, Oguma K, Imai H, Takamizu A, Koizumi A, Yoshida K. Fetal growth restriction as the initial finding of preeclampsia is a clinical predictor of maternal and neonatal prognoses: a single-center retrospective study. *BMC pregnancy and childbirth*. 2021 Dec;21:1-8. doi: 10.1186/s12884-021-04152-2.
- 96.Kusumaningrum RY, Murti B, Prasetya H. Low birth, prematurity, and pre-eclampsia as risk factors of neonatal asphyxia. *Journal of Maternal and Child Health*. 2019 Jan 1;4(1):49-54. doi: 0.26911/thejmch.2019.04.01.07.
- 97.Luo R, Wang Y, Xu P, Cao G, Zhao Y, Shao X, Li YX, Chang C, Peng C, Wang YL. Hypoxia-inducible miR-210 contributes to preeclampsia via targeting thrombospondin type I domain containing 7A. *Scientific reports*. 2016 Jan 22;6(1):19588. doi: 10.1038/srep19588.
- 98.Gunel T, Zeybek YG, Akçakaya P, Kalelioglu I, Benian A, Ermis H, Aydinli K. Serum microRNA expression in pregnancies with preeclampsia. *Genet Mol Res*. 2011 Oct;10(4):4034-40. doi: 10.4238/2011.November.8.5.
- 99.Ghafari A, Lessan pezeshki M, Saffari M. P0069 MICRO RNA 155, 210, 494, 29B AND 34A EXPRESSION PROFILE IN PREECLAMPSIA AND

NORMAL PREGNANCIES. Nephrology Dialysis Transplantation. 2020 Jun 1;35(Supplement_3):gfaa142-P0069. doi: 10.1093/ndt/gfaa142.P0069.

100. Namavar JB, RAFIEI S. Coagulation factors in severe preeclampsia. Corpus ID: 30156455.
101. MG N. Perinatal outcomes in preeclampsia that is complicated by massive proteinuria. Am J Obstet Gynecol. 2003;188:264-8. Doi: 10.1067/mob.2003.84.
102. Dacaj R, Izetbegovic S, Stojkanovic G, Dreshaj S. Elevated liver enzymes in cases of preeclampsia and intrauterine growth restriction. medical archives. 2016 Jan 31;70(1):44. doi: 10.5455/medarh.2016.70.44-47.
103. Thangaratinam S, Koopmans CM, Iyengar S, Zamora J, Ismail KM, Mol BW, Khan KS, TIPPS (Tests in Prediction of Preeclampsia's Severity) Review Group. Accuracy of liver function tests for predicting adverse maternal and fetal outcomes in women with preeclampsia: a systematic review. Acta obstetrica et gynecologica Scandinavica. 2011 Jun;90(6):574-85. doi: 10.1111/j.1600-0412.2011.01112.x.

ANNEXURES

CONSENT FORM

B.L.D.E (DEEMED TO BE UNIVERSITY) SHRI B M PATIL MEDICAL COLLEGE HOSPITAL AND RESEARCH CENTER, BIJAPUR-586103

INFORMED CONSENT FOR PARTICIPATION IN DISSERTATION/RESEARCH

I, the undersigned, _____, D/O W/O _____, aged _____ years, ordinarily resident of _____ do hereby state/declare that Dr KOTA SAI MEGHANA of Shri. B. M. Patil Medical College Hospital and Research Centre have examined me thoroughly on at _____ (place) and it has been explained to me in my own language about the intervention being performed on me, its progression and possible complications. Further, Dr. KOTA SAI MEGHANA informed me that he/she is conducting a dissertation/research titled "EVALUATION OF MicroRNA 21 0 AS PROGNOSTIC BIOMARKER OF PRE-ECLAMPSIA – A CASE - CONTROL STUDY" under the guidance of Dr. RAJASRI. G. YALI WAL requesting my participation in the study. The doctor has also informed me that during the conduct of this procedure, adverse results may be encountered. Among the above complications, most of them are treatable but are not anticipated hence there is a chance of aggravation of my condition and in rare circumstances, it may prove fatal despite the anticipated diagnosis and best treatment made available. Further Doctor has informed me that my participation in this study would help in the evaluation of the results of the study which is a useful reference to the treatment of

other similar cases shortly, and also, I may be benefited in getting relieved of suffering or cure of the disease I am suffering.

The Doctor has also informed me that information given by me, observations made, photographs and video graphs taken upon me by the investigator will be kept secret and not assessed by a person other than my legal hirer or me except for academic purposes. The Doctor did inform me that though my participation is purely voluntary, based on the information given by me, I can ask for any clarification during the course of treatment/study related to diagnosis, the procedure of treatment, result of treatment, or prognosis. At the same time, I have been informed that I can withdraw from my participation in this study at any time if I want or the investigator can terminate me from the study at any time study but not the procedure of treatment and follow-up unless I request to be discharged. After understanding the nature of dissertation or research, diagnosis made, mode of treatment, I the undersigned Smt under my full conscious state of mind agree to participate in the said research/ dissertation.

Signature of patient:

Signature of Doctor:

Date:

Place:

B.L.D.E (DEEMED TO BE UNIVERSITY)

ಶ್ರೀ ಬಿ.ಎಂ.ಪಟ್ಟೇಲ್ ಮೆಡಿಕಲ್ ಕಾಲೇಜು, ಆಸ್ಪತ್ರೆ ಮತ್ತು ಸಂಶೋಧನಾ ಕೇಂದ್ರ, ವಿಜಯಪುರ-586103

ಪ್ರಬಂಧ/ಸಂಶೋಧನೆಯಲ್ಲಿ ಪಾಲ್ಗೊಳ್ಳಲು ಮಾಹಿತಿ ಪಡೆದ ಸಮ್ಮತಿ

ನಾನು, ಕೆಳಗಿನವರು _____ ಸಹಿಯಿಟ್ಟವರು, ಮಗ/ಮಗಳು/ಪತ್ನಿಯ _____ ವಯಸ್ಸು _____ ವರ್ಷಗಳು, ಸಾಮಾನ್ಯವಾಗಿ ನಿವಾಸಿಸುವ ಸ್ಥಳದ ಹೆಸರು _____, ಇಲ್ಲಿ ಹೇಳಿದ್ದೇನೆ/ಘೋಷಿಸುತ್ತೇನೆ ಡಾಕ್ಟರ್ ಹೆಸರು _____ ಅವರು ಆಸ್ಪತ್ರೆ ಹೆಸರು _____ ಅವರು ನನ್ನನ್ನು ಪೂರ್ಣವಾಗಿ ಪರೀಕ್ಷಿಸಿದರು ದಿನಾಂಕದಲ್ಲಿ _____ ಸ್ಥಳ ಹೆಸರು _____ ಮತ್ತು ನನಗೆ ನನ್ನ ಭಾಷೆಯಲ್ಲಿ ವಿವರಿಸಲಾಗಿದೆ ನಾನು ಒಂದು ರೋಗ (ಸ್ಥಿತಿ) ಅನುಭವಿಸುತ್ತಿದ್ದೇನೆ. ಮುಂದುವರಿದು ಡಾಕ್ಟರ್ ನನಗೆ ತಿಳಿಸಿದ್ದಾರೆ ಅವರು ಒಂದು ಪದ್ಧತಿ/ಸಂಶೋಧನೆ ನಡೆಸುತ್ತಿದ್ದಾರೆ ಶೀರ್ಷಿಕೆಯುಳ್ಳ _____ ಡಾಕ್ಟರ್ _____ ಮಾರ್ಗದರ್ಶನದಲ್ಲಿ ನನ್ನ ಪಾಲ್ಗೊಳ್ಳುವಿಕೆಯನ್ನು ಕೇಳಿದ್ದಾರೆ ಅಧ್ಯಯನದಲ್ಲಿ.

ಡಾಕ್ಟರ್ ನನಗೆ ಇದನ್ನು ಕೂಡಾ ತಿಳಿಸಿದ್ದಾರೆ ಈ ಕ್ರಮದ ನಡೆವಳಿ ಪ್ರತಿಕೂಲ ಫಲಿತಾಂಶಗಳನ್ನು ಎದುರಿಸಬಹುದು. ಮೇಲೆ ಹೇಳಿದ ಪ್ರಕಟಣೆಗಳಲ್ಲಿ, ಅಧಿಕಾಂಶವು ಚಿಕಿತ್ಸಿಸಬಹುದಾದರೂ ಅದನ್ನು ನಿರೀಕ್ಷಿಸಲಾಗುತ್ತಿಲ್ಲ ಆದ್ದರಿಂದ ನನ್ನ ಸ್ಥಿತಿಯ ಹಿರಿದಾಗುವ ಅವಕಾಶವಿದೆ ಮತ್ತು ಅಪರೂಪದ ಸಂದರ್ಭಗಳಲ್ಲಿ ಅದು ಮರಣಕಾರಕವಾಗಿ ಪರಿಣಮಿಸಬಹುದು ಹೊಂದಿದ ರೋಗನಿರ್ಧಾರ ಮತ್ತು ಯಥಾಶಕ್ತಿ ಚಿಕಿತ್ಸೆ ಮಾಡಲು ಹೊಂದಿದರೂ. ಮುಂದುವರಿದು ಡಾಕ್ಟರ್ ನನಗೆ ತಿಳಿಸಿದ್ದಾರೆ ನನ್ನ ಪಾಲ್ಗೊಳ್ಳುವಿಕೆ ಈ ಅಧ್ಯಯನದ ಫಲಿತಾಂಶಗಳ ಮೌಲ್ಯಮಾಪನದಲ್ಲಿ ಸಹಾಯಕವಾಗುತ್ತದೆ ಇತರ ಸಮಾನ ಪ್ರಕರಣಗಳ ಚಿಕಿತ್ಸೆಗೆ ಉಪಯುಕ್ತ ಉಲ್ಲೇಖವಾಗಿದೆ, ಮತ್ತು ನಾನು ಅನುಭವಿಸುವ ರೋಗದಿಂದ ವಿಮುಕ್ತಿ ಅಥವಾ ಗುಣಮುಖಗೊಳ್ಳುವಲ್ಲಿ ನನಗೆ ಪ್ರಯೋಜನವಾಗಬಹುದು.

ಡಾಕ್ಟರ್ ನನಗೆ ಇದನ್ನು ಕೂಡಾ ತಿಳಿಸಿದ್ದಾರೆ ನನ್ನಿಂದ ನೀಡಿದ ಮಾಹಿತಿ, ಮಾಡಿದ ಪರಿಶೀಲನೆಗಳು / ಫೋಟೋಗ್ರಾಫ್‌ಗಳು / ವೀಡಿಯೋ ಗ್ರಾಫ್‌ಗಳು ನನ್ನ ಮೇಲೆ ತೆಗೆದುಕೊಳ್ಳಲಾಗುವ ಅನ್ವೇಷಕರು ರಹಸ್ಯವಾಗಿ ಇಡುವರು ಮತ್ತು ನಾನು ಅಥವಾ ನನಗೆ ಕಾನೂನು ದೃಷ್ಟಿಯಲ್ಲಿ ಸಂಬಂಧಿತರನ್ನು ಹೊರತುಪಡಿಸಿ ಇತರ ವ್ಯಕ್ತಿಯಿಂದ

ಮೌಲ್ಯಮಾಪನ ಮಾಡಲಾಗುವುದಿಲ್ಲ. ಡಾಕ್ಟರ್ ನನಗೆ ತಿಳಿಸಿದ್ದಾರೆ ನನ್ನ ಪಾಲ್ಗೊಳ್ಳುವಿಕೆ ಶುಧ್ಧವಾಗಿ ಸ್ವೇಚ್ಛಾಯಿತ,
ನನ್ನಿಂದ ನೀಡಿದ ಮಾಹಿತಿಯ ಆಧಾರದ ಮೇಲೆ, ಚಿಕಿತ್ಸೆ / ಅಧ್ಯಯನದ ಸಂಬಂಧದಲ್ಲಿ ರೋಗನಿರ್ಧಾರ, ಚಿಕಿತ್ಸೆಯ
ವಿಧಾನ, ಚಿಕಿತ್ಸೆಯ ಫಲಿತಾಂಶ ಅಥವಾ ಆ ಭವಿಷ್ಯದ ಪ್ರವೃತ್ತಿಗಳು ಬಗ್ಗೆ ಯಾವುದೇ ಸ್ಪಷ್ಟತೆ ಕೇಳಬಹುದು. ಅದೇ
ಸಮಯದಲ್ಲಿ ನನಗೆ ತಿಳಿಸಲಾಗಿದೆ ನಾನು ಯಾವುದೇ ಸಮಯದಲ್ಲಿ ಈ ಅಧ್ಯಯನದಲ್ಲಿ ನನ್ನ ಪಾಲ್ಗೊಳ್ಳುವಿಕೆಯನ್ನು
ನಿಲ್ಲಿಸಬಹುದು ನಾನು ಬಯಸಿದರೆ ಅಥವಾ ಅನ್ವೇಷಕರು ಅಧ್ಯಯನದಿಂದ ಯಾವುದೇ ಸಮಯದಲ್ಲಿ ನನ್ನನ್ನು
ನಿಲ್ಲಿಸಬಹುದು.

ಪ್ರಬಂಧ ಅಥವಾ ಸಂಶೋಧನೆಯ ಸ್ವಭಾವ, ಮಾಡಿದ ರೋಗನಿರ್ಧಾರ ಮತ್ತು ಚಿಕಿತ್ಸೆಯ ವಿಧಾನವನ್ನು
ಅರ್ಥಮಾಡಿಕೊಂಡು, ನಾನು ಕೆಳಗಿನ ಶ್ರೀ / ಶ್ರೀಮತಿ _____ ನನ್ನ ಪೂರ್ಣವಾದ ಪ್ರಜ್ಞೆಯ ಸ್ಥಿತಿಯಲ್ಲಿ
ಹೇಳಿದ ಸಂಶೋಧನೆ / ಪ್ರಬಂಧದಲ್ಲಿ ಪಾಲ್ಗೊಳ್ಳಲು ಒಪ್ಪುತ್ತೇನೆ.

ರೋಗಿಯ ಸಹಿ

ಡಾಕ್ಟರನ

ಸಹಿ

ಸಾಕ್ಷಿಗಳು

1)

2)

PROFORMA

“EVALUATION OF miRNA 210 AS PROGNOSTIC BIOMARKER OF PRE-ECLAMPSIA – A CASE-CONTROL STUDY”

CASE NO. -

NAME -

DATE OF ADMISSION -

IP NUMBER -

AGE/SEX -

PHONE NUMBER -

ADDRESS -

CHIEF COMPLAINTS –

OBSTETRIC HISTORY – G P L A

MARITAL HISTORY -

LAST MENSTRUAL PERIOD -

EXPECTED DATE OF DELIVERY -

PERIOD OF GESTATION –

ACCORDING TO EARLY PREG. SCAN –

EXPECTED DATE OF DELIVERY –

PERIOD OF GESTATION –

A.N.C -

1ST TRIMESTER -

2ND TRIMESTER -

3RD TRIMESTER -

RELATED DRUG HISTORY -

PAST HISTORY –

PERSONAL HISTORY –

GENERAL PHYSICAL EXAMINATION -

HEIGHT -

WEIGHT -

B.M.I. -

TEMPERATURE -

PULSE -

BLOOD PRESSURE -

CARDIOVASCULAR SYSTEM -

RESPIRATORY SYSTEM -

PER ABDOMEN -

P/S -

P/V –

ANY ANTENATAL OR INTRAPARTUM COMPLICATION-

- PIH
- ABRUPTION
- ANTEPARTUM ECLAMPSIA
- POLYHYDRAMNIOS
- TWINS
- DIABETES /GDM
- ANAEMIA- MILD/MODERATE/SEVERE
- ANY OTHER-

PALLOR
ICTERUS
CYANOSIS
CLUBBING
LYMPHADENOPATHY
PEDAL EDEMA
BSUA

DIAGNOSIS –

CLINICAL FINDINGS-

- BLOOD PRESSURE -
- MAP -
- RENAL FUNCTION TEST –

Blood Urea
Serum Creatinine
Uric Acid
Serum Calcium
Serum Phosphorus
Serum Sodium
Serum Potassium
Serum Chloride

- COMPLETE BLOOD COUNT –

Hb
TC
Platelets

➤ LIVER FUNCTION TEST –

Total Serum Bilirubin
Conjugated
Unconjugated
SGPT
SGOT
Serum Protein
Albumin
Globulin
AG Ratio
ALP

➤ FUNDOSCOPY -

✓ **FETAL OUTCOME -**

- DOPPLER STUDY -
- MCA-
- UMBILICAL ARTERY -
- AMNIOTIC FLUID INDEX -
- FETAL GROWTH RESTRICTION -
- ABDOMINAL CIRCUMFERENCE -
- BI-PARIETAL DIAMETER -
- FEMORAL LENGTH -
- HEAD CIRCUMFERENCE -
- COMPLETE BLOOD COUNT –

➤ COAGULATION PROFILE -

APTT Test
APTT Control
PT Test
PT Control
INR

OBSTETRIC OUTCOME -

- TIME OF DELIVERY -
- DURATION OF SECOND STAGE OF LABOUR -
- FINAL OUTCOME - Normal delivery/
Instrumental delivery/ LSCS
- IF L.S.C.S, THEN INDICATION -

NEONATAL OUTCOME**BABY DETAILS -**

- GENDER -
- DATE OF DELIVERY -
- TIME OF DELIVERY -
- BIRTH WEIGHT -
- APGAR SCORE AT 1MIN AND 5MIN -

➤ IF ANY RESPIRATORY DISTRESS
WITHIN 24HOURS -

(Yes/ No) -

➤ NICU ADMISSION (Yes/ No) -

If yes, why?

➤ DURATION OF STAY -

➤ NEONATAL DEATH -

If yes, why?

ETHICAL CLEARANCE



BLDE
(DEEMED TO BE UNIVERSITY)
Declared as Deemed to be University u/s 3 of UGC Act, 1956
Accredited with 'A' Grade by NAAC (Cycle-2)
The Constituent College



SHRI B. M. PATIL MEDICAL COLLEGE, HOSPITAL & RESEARCH CENTRE, VIJAYAPURA
BLDE (DU)/IEC/ 891/2022-23 10/4/2023

INSTITUTIONAL ETHICAL CLEARANCE CERTIFICATE

The Ethical Committee of this University met on **Saturday, 18th March, 2023 at 11.30 a.m. in the CAL Laboratory, Dept. of Pharmacology**, scrutinizes the Synopsis/ Research Projects of Post Graduate Student / Under Graduate Student /Faculty members of this University /Ph.D. Student College from ethical clearance point of view. After scrutiny, the following original/ corrected and revised version synopsis of the thesis/ research projects has been accorded ethical clearance.

TITLE: "EVALUATION OF miRNA-210 AS PROGNOSTIC BIOMARKER OF PRE-ECLAMPSIA- A CASE-CONTROL STUDY".

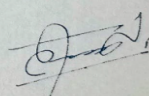
NAME OF THE STUDENT/PRINCIPAL INVESTIGATOR: DR.KOTA SAI MEGHANA

**NAME OF THE GUIDE: DR.RAJASRI G. YALIWAL, PROFESSOR,
DEPT. OF OBSTETRICS AND GYNAECOLOGY**



Dr.Santoshkumar Jeevanagi
Chairperson
IEC-SBMPMC,
VIJAYAPURA

Chairman,
Institutional Ethical Committee,
BLDE (Deemed to be University)
Vijayapura



Dr.Akram A. Naikawadi
Member Secretary
IEC-SBMPMC,
VIJAYAPURA
MEMBER SECRETARY
Institutional Ethics Committee
BLDE (Deemed to be University)
Vijayapura-586103, Karnataka

Following documents were placed before Ethical Committee for Scrutinization.

- Copy of Synopsis/Research Projects
- Copy of inform consent form
- Any other relevant document

Smt. Bangaramma Sajjan Campus, B. M. Patil Road (Sholapur Road), Vijayapura - 586103, Karnataka, India.
BLDE (DU): Phone: +918352-262770, Fax: +918352-263303, Website: www.bldedu.ac.in, E-mail: office@bldedu.ac.in
College: Phone: +918352-262770, Fax: +918352-263019, E-mail: bmpmc.principal@bldedu.ac.in

CLINICAL TRIAL REGISTRATION

CTRI No	CTRI/2023/10/059019 [Registered on: 23/10/2023] Trial Registered Prospectively	
Acknowledgement Number	REF/2023/06/068680	
Last Modified On:	24/03/2025	
Post Graduate Thesis	Yes	
Type of Trial	Observational	
Type of Study Clarification(s) with Reply Modification(s)	Case Control Study	
Study Design	Other	
Public Title of Study	Evaluation of miRNA -210 as prognostic marker of pre-eclampsia	
Scientific Title of Study Clarification(s) with Reply Modification(s)	EVALUATION OF miRNA - 210 AS PROGNOSTIC BIOMARKER OF PRE-ECLAMPSIA - A CASE CONTROL STUDY	
Trial Acronym		
Secondary IDs if Any	Secondary ID	Identifier
	NIL	NIL
Details of Principal Investigator or overall Trial Coordinator (multi-center study) Clarification(s) with Reply Modification(s)	Name	DR KOTA SAI MEGHANA
	Designation	PG STUDENT
	Affiliation	SHRI B M PATIL MEDICAL COLLEGE HOSPITAL AND RESEARCH CENTRE
	Address	OPD NO 2 SHRI B M PATIL MEDICAL COLLEGE HOSPITAL AND RESEARCH CENTRE SHRI BANGARAMMA SAJJAN CAMPUS VIJAYAPURA OPD NO 2 SHRI B M PATIL MEDICAL COLLEGE HOSPITAL AND RESEARCH CENTRE SHRI BANGARAMMA SAJJAN CAMPUS VIJAYAPURA 586103 Bijapur KARNATAKA 586103 India
	Phone	7032974806
	Fax	
	Email	kotameghana7@gmail.com
	Name	DR RAJASRI G YALIWAL
	Designation	ASSOCIATE PROFESSOR
	Affiliation	SHRI B M PATIL MEDICAL COLLEGE HOSPITAL AND RESEARCH CENTRE

161

PLAGIARISM

Meghana Kota
final thesis.docx

BLDE University

Document Details

Submission ID
trn:oid:::3618:87576960

Submission Date
Mar 24, 2025, 6:07 PM GMT+5:30

Download Date
Mar 24, 2025, 6:12 PM GMT+5:30

File Name
final thesis.docx

File Size
5.3 MB

115 Pages
17,923 Words
102,720 Characters

iThenticate Page 1 of 121 - Cover Page

Submission ID trn:oid:::3618:87576960

iThenticate Page 2 of 121 - Integrity Overview

Submission ID trn:oid:::3618:87576960

6% Overall Similarity

The combined total of all matches, including overlapping sources, for each database.

Filtered from the Report

- Quoted Text
- Small Matches (less than 10 words)

Exclusions

- 2 Excluded Websites

Match Groups

- 74 Not Cited or Quoted 6%
Matches with neither in-text citation nor quotation marks
- 4 Missing Quotations 0%
Matches that are still very similar to source material
- 0 Missing Citation 0%
Matches that have quotation marks, but no in-text citation
- 0 Cited and Quoted 0%
Matches with in-text citation present, but no quotation marks

Top Sources

- 5% Internet sources
- 3% Publications
- 0% Submitted works (Student Papers)

Integrity Flags

0 Integrity Flags for Review
No suspicious text manipulations found.

Our system's algorithms look deeply at a document for any inconsistencies that would set it apart from a normal submission. If we notice something strange, we flag it for you to review.

A Flag is not necessarily an indicator of a problem. However, we'd recommend you focus your attention there for further review.