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Gynecology & Obstetrics



Infiltration of Leukocytes

Thrombocytopenia in Pregnancy

Highlights

Efficacy of Tranexamic Acid

Intravenous Ferric Carboxymaltose

Discovering Thoughts, Inventing Future

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Efficacy of Tranexamic Acid in Decreasing Blood Loss during and after Cesarean Section

By Dr. Dipu Das, Prof. Dr. Shamsun Nahar Begum, Prof. Namita Rani Sinha, Dr. Barnali Sinha & Dr. Nasrin Akhter

Abstract- Background: Tranexamic acid (TXA) is an anti-fibrinolytic agent. Its use in primary TKR is supported by many studies that confirmed its efficacy for decreasing blood loss. Cesarean section rates are increasing all over the world. Per partum hemorrhage is one of the most common, life-threatening complications of this procedure. The aim of the study to find out the efficacy of tranexamic acid in decreasing blood loss during and after cesarean section.

Methodology: The present study was performed at the Department of Obstetrics and Gynecology of the AL Haramine Hospital, Sylhet, from June 1, 2017, to November 30, 2017. Subjects were eligible for the trial if the fetus was more than 38 weeks estimated gestational age and they required elective CS. Elective CS was defined as CS performed before the onset of labor.

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Efficacy of Tranexamic Acid in Decreasing Blood Loss during and after Cesarean Section

Dr. Dipu Das [α], Prof. Dr. Shamsun Nahar Begum [σ], Prof. Namita Rani Sinha [ρ], Dr. Barnali Sinha [ω] & Dr. Nasrin Akhter [¥]

Abstract- Background: Tranexamic acid (TXA) is an anti-fibrinolytic agent. Its use in primary TKR is supported by many studies that confirmed its efficacy for decreasing blood loss. Cesarean section rates are increasing all over the world. Per partum hemorrhage is one of the most common, life-threatening complications of this procedure. The aim of the study to find out the efficacy of tranexamic acid in decreasing blood loss during and after cesarean section.

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Results: Mean hematocrit after surgery was 34.8±2.9 percent in tranexamic acid group and 32.3±3.3 percent in placebo group ($p>0.05$). Which were statistically significant between two groups (Table III). Compare the incidence of post-partum hemorrhage (PPH) between both study and control groups, it was found that the incidence of post-partum hemorrhage (≥500mL) was more in the control group than in the study group (p-value = 0.032).

Conclusion: Mean hematocrit after surgery was not statistically significant in tranexamic acid group than placebo group. Compare the incidence of post-partum hemorrhage (PPH) between both study and control groups, it was found that the incidence of post-partum hemorrhage was more in the control group than in the study group.

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I. Introduction

Tranexamic acid (TXA) is an anti-fibrinolytic agent. Its use in primary TKR is supported by many studies that confirmed its efficacy for decreasing blood loss.[1] Cesarean section rates are increasing all over the world. Per partum hemorrhage is one of the most common, life-threatening complications of this procedure.[2]

The WHO estimates that PPH accounts for nearly 30% of maternal deaths worldwide with an estimated 20million cases annually.[3] In order to reduce maternal morbidity and mortality caused by bleeding, it is important to reduce the amount of bleeding during and after lower segment cesarean section. A popular approach is to minimize peri operative bleeding through the prophylactic use of antifibrinolytic agents such as aprotinin, tranexamic acid and amino caproic acid.[3] Reducing bleeding during and after caesarian directly improve the outcomes of cesarean delivery, especially maternal mortality and morbidity. Tranexamic acid is a fibrinolysis inhibitor that has been used for many years to reduce bleeding in various surgical procedures.

II. Methodology

The present study was performed at the Department of Obstetrics and Gynecology of the AL Haramine Hospital, Sylhet, from June 1, 2017, to November 30, 2017. Subjects were eligible for the trial if the fetus was more than 38 weeks estimated gestational age and they required elective CS. Elective CS was defined as CS performed before the onset of labor. Women were excluded if they had risk factors associated with an increased risk of postpartum hemorrhage (PPH) such as anemia (hemoglobin <7 g%), multiple gestation, antepartum hemorrhage (placenta previa or placental abruption), abnormal placentation (accreta, increta, or percreta), uterine fibroids, polyhydramnios, emergency CS, a history of uterine atony and postpartum bleeding, and a current or previous history of significant disease, including heart disease, liver, renal disorders, or a known coagulopathy. Following informed consent, simple randomization using a random number table was performed by the investigational pharmacy staff, who took no further part in the study. Infusion bags were prepared and labeled as bag A (TA group) containing 1 g/10 mL TA

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(Transamin, Fako Ilacları A.S., Istanbul, Turkey) diluted with 20 mL of 5% glucose, and bag B (placebo group) containing 30 mL of 5% glucose. Providers and patients were blinded to the contents of the bags until the conclusion of the study.

TA or placebo was slowly administered intravenously over a 5-minute period at least 10 minute prior to skin incision. After delivery, both groups received a 5 IU intravenous bolus of preprepared oxytocin, and then 30 IU oxytocin in 500 mL lactated Ringer's solution was infused at a rate of 125 mL/h. An antibiotic, 1 g cefazolin diluted in 20 mL normal saline, was administered over a 5-minute period. Vital signs (heart rate, blood pressure, and respiratory rate) were checked and noted before the operation, immediately after placental delivery, and 1 and 2 hours after birth. Prothrombin time (PT), active prothrombin time (aPTT), and complete blood count (CBC) were performed before delivery and on the second day after delivery. Estimated blood loss was calculated using the difference in hematocrit values taken prior to and 48 hour after cesarean delivery, according to the following formula:

$$\text{Estimated blood loss} = \text{EBV} \times \frac{\text{Preop hematocrit} _ \text{Postop hematocrit}}{\text{Preop hematocrit}}$$

where EBV (estimated blood volume) in mL¼ the woman's weight in kg_85.14 Blood loss >1000 mL during the procedure was defined as excessive bleeding. After discharge, women who received TA were instructed about the signs and symptoms of a thromboembolic event, given written instruction sheets with a diary for symptom documentation, and instructed to contact one of the coauthors (O.A. or O.C.) immediately if any listed symptom occurred. Women who complained of symptoms were examined by one of the coauthors. All participants and babies were examined for thromboembolic events 3 and 6 weeks after surgery. The primary outcome was the estimated blood loss during CS. Other outcomes were excessive bleeding (defined as an estimated blood loss >1000 mL), the need for blood transfusion, the use of additional uterotonic agents indicating atony (such as an oxytocin infusion or prostaglandin F2a), TA side effects (such as nausea, vomiting, or diarrhea), duration of the mother's postnatal hospital stay, and neonatal outcome.

III. Results

The subject characteristics in the two groups were similar with no statistically significant difference between age, height, weight, gestational age, gravida and duration of surgery (Table I). The heart rate, respiratory rate, systolic BP and diastolic BP in both the Tranexamic acid and Placebo groups, Immediate after placental delivery, 1 hour after placental delivery and 2 hours after placental delivery, it was found that there was no significant statistical difference (Table-II). Mean hemoglobin after surgery was 8.7±0.7 g/dl and 8.1±0.8 g/dl in tranexamic acid and placebo group respectively (p>0.05). Mean hematocrit after surgery was 34.8±2.9 percent in tranexamic acid group and 32.3±3.3 percent in placebo group (p>0.05). Which were statistically significant between two groups (Table III). Compare the incidence of post-partum hemorrhage (PPH) between both study and control groups, it was found that the incidence of post-partum hemorrhage ≱500mL) was more in the control group than in the study group (p-value = 0.032) (Table -IV).

Table I: Demographic characteristics of participants.

	Tranexamic acid (n=50)	Placebo (n=50)	p value
	Mean±SD	Mean±SD	
Age (years)	24.1±3.8	24.7±4.0	0.444^{ns}
Height (cm)	154.2±4.1	155.6±4.3	0.099^{ns}
Weight (kg)	66.6±6.9	64.7±8.8	0.233^{ns}
Gestational age (weeks)	38.3±1.0	38.4±0.7	0.564^{ns}
Gravidity	2.1±0.7	2.0±0.9	0.537^{ns}
Duration of surgery (min)	44.8±2.6	44.7±2.7	0.851^{ns}

ns= not significant

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Table II: Vital signs after placental delivery

	Tranexamic acid (n=50)	Placebo (n=50)	p value
	Mean±SD	Mean±SD	
Immediate after placental delivery			
HR (beat/min)	90.4±9.0	92.9±8.7	0.161^{ns}
RR (breaths/min)	19.1±4.9	20.5±3.2	0.093^{ns}
SBP (mmHg)	120.6±10.8	124.1±11.8	0.125^{ns}
DBP (mmHg)	76.0±10.1	79.3±9.8	0.100^{ns}
One hour after placental delivery			
HR (beat/min)	92.0±9.1	88.7±8.9	0.070^{ns}
RR (breaths/min)	20.2±6.1	21.9±5.2	0.137^{ns}
SBP (mmHg)	127.2±9.2	124.4±11.1	0.173^{ns}
DBP (mmHg)	78.5±8.7	80.3±10.6	0.356^{ns}
Two hours after placental delivery			
HR (beat/min)	91.4±10.2	89.3±8.4	0.264^{ns}
RR (breaths/min)	19.8±5.6	20.1±3.3	0.745^{ns}
SBP (mmHg)	124.6±11.5	124.1±12.0	0.832^{ns}
DBP (mmHg)	79.2±8.1	79.4±8.1	0.902^{ns}

ns= not significant

Table III: Comparison of haemoglobin and hematocrit before and 24 h after the surgery in the tranexamic and placebo groups

	Tranexamic acid (n=50)	Placebo (n=50)	P value
	Mean±SD	Mean±SD	
Hemoglobin (g/dl)			
Before CS	9.8±0.8	9.7±1.0	0.582^{ns}
After CS	8.7±0.7	8.1±0.8	0.001^{s}
Hematocrit (%)			
Before CS	35.0±2.6	34.1±1.9	0.051^{ns}
After CS	34.8±2.9	32.3±3.3	0.001^{s}

s= significant, ns= not significant

Table IV: Comparison of amount of blood loss (PPH) in the tranexamic and placebo groups.

Blood loss from placental delivery to 2 hours postpartum (ml)	Tranexamic acid (n=50)		Placebo (n=50)		p value
	n	%	n	%	
<500mL	43	86.0	34	68.0	0.032^{s}
≥500mL	7	14.0	16	32.0	

IV. Discussion

In this present study it was observed that two groups were similar with no statistically significant difference between age, height, weight, gestational age, gravida and duration of surgery.

In this current study it was observed that heart rate, respiratory rate, systolic BP and diastolic BP in both the Tranexamic acid and Placebo groups, Immediate after placental delivery, 1 hour after placental delivery and 2 hours after placental delivery, it was found that there was no significant statistical difference. Similar study carried out by Ming-ying Gai et al[4] in China showed that tranexamic acid significantly reduces bleeding from the time of placental delivery to 2 hours post partum. The study showed significant decrease in the incidence of > 500 ml blood loss in the study group as compared to control group (P-0.029). Zheng et al[5], showed similar results after vaginal delivery.

In this study it was observed that mean hemoglobin after surgery was 8.7±0.7 g/dl and 8.1±0.8 g/dl in tranexamic acid and placebo group respectively (p>0.05). Mean hematocrit after surgery was 34.8±2.9 percent in tranexamic acid group and 32.3±3.3 percent in placebo group (p>0.05). Which were statistically significant between two groups. Sekhavat et al.[6] in their prospective study on 90 primi gravidae undergoing CS, found a decrease of blood loss from the end of lower segment CS to 2 h postpartum of only 9 ml (28 versus 37.12 ml in TA and control groups, respectively).

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However, they found that this reduction was statistically significant.[6] This finding has not been described in other studies.[7,8]

In this series it was observed that compare the incidence of post-partum hemorrhage (PPH) between both study and control groups, it was found that the incidence of post-partum hemorrhage (≥500mL) was more in the control group than in the study group (p-value = 0.032). An estimated blood loss in excess of 500 ml following a vaginal birth or a loss of greater than 1000 ml following caesarean birth has been used for the diagnosis of postpartum hemorrhage.[9] Assessment of blood loss during cesarean delivery is typically underestimated.[10] The most commonly used methods for such assessment are the visual estimation method, the mathematical calculation measuring the hematocrit (Hct) prior to and 1 h postoperatively and the swab weighing method. The visual estimation method is notoriously inaccurate[11]; Villeneuve et al. found that obstetricians assessed blood loss inaccurately during CS; an underestimation up to 579 ml[12]. Brecher et al. found that blood loss calculated using Hct as a variable gave an average 2.1 times overestimation of intraoperative blood loss compared to visual estimation.[10] The drawbacks of using Hct for calculation of blood loss include the use of body weight in the mathematical calculation which is misleading during pregnancy and the possible bias resulting from hemodilution from the intraoperative fluids given during the operation.[13] Similar study carried out in India by Mayur et al.[14] showed comparable results reducing the blood loss in the study group. Another study carried out by Ming-Ying et al., in China showed that TXA significantly reduces bleeding from the time of placental delivery to the end of caesarean section, which was 351 mL in the study group while 440 mL in the control group.[15] Zheng et al. showed similar results after vaginal delivery; there was significantly less blood loss in the TXA group (243 mL) when compared to those who receive no treatment (309 mL).[16]

V. Conclusion

Mean hematocrit after surgery was not statistically significant in tranexamic acid group than placebo group. Compare the incidence of post-partum hemorrhage (PPH) between both study and control groups, it was found that the incidence of post-partum hemorrhage was more in the control group than in the study group.

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Alterations of Non Invasive Hemodynamics in Weeks 10 to 14 of Gestation Associated with Preeclampsia and Adverse Perinatal Results

By Berenice Zavala Barrios, Juan Manuel Veléz Reséndiz, Mónica Malagón Gomez, Peña Vega Cynthia & Jesus Carlos Briones Garduño

Abstract- *Objective:* To study the association of placental adaptation of perinatal outcomes with hemodynamic values measured with USCOM.

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Keywords: *maternal hemodynamics, adverse perinatal outcome, preeclampsia, gestational diabetes, perinatal death.*

GJMR-E Classification: *NLMC Code: WG 106*



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Alterations of Non Invasive Hemodynamics in Weeks 10 to 14 of Gestation Associated with Preeclampsia and Adverse Perinatal Results

Alteraciones De Hemodinámica No Invasiva En Las Semanas 10 A 14 De La Gestación Asociada A Preeclampsia Y Resultados Perinatales Adversos

Berenice Zavala Barrios [α], Juan Manuel Veléz Reséndiz [σ], Mónica Malagón Gomez [ρ], Peña Vega Cynthia [ω] & Jesus Carlos Briones Garduño [¥]

Resumen- Objetivo: Estudiar la asociación de la adaptación placentaria de los resultados perinatales con los valores hemodinámicos medidos con USCOM.

Métodos: Estudio de casos y controles anidado en una cohorte. Medimos GC, IC, RVP e IRVP con hemodinámica no invasiva, al final del embarazo se registró el resultado perinatal. El análisis estadístico se realizó con la curva ROC para puntos de corte, tablas de contingencia, reacción extrema y regresión lineal.

Resultados: N: 93 pacientes, los puntos de corte fueron GC 5.5lt., IC3 lt., RVP 1200din e IRVP 2500din. El IC <2.5lt. OR = 2.4 para desarrollar un resultado perinatal adverso (p <0.049), el 100% de la preeclampsia tenía IC> 3lt. En regresión lineal para evaluar RVP y GC, con presencia de preeclampsia r2 = 0,857 (p <0,008); diabetes gestacional r2 = 0.865, (p <0.05); Resultado perinatal adverso r2 = 0.803, (p <0.05); y muerte perinatal r2 = 0.969, (p <0.011). IC <3lt e IRVP> 2500din.

Discusión: A diferencia de lo que se informó, establecimos puntos de corte para realizar subgrupos que demuestran asociación con preeclampsia, diabetes gestacional, resultado perinatal adverso y muerte perinatal.

Conclusiones: IC <3lt obtuvo una sensibilidad del 78% y una especificidad del 66% para detectarresultados perinatales adversos (OR 1.46) y OR 2.4 para desarrollar diabetes gestacional y100% de preeclampsia. RVP> 1200din., IRVP> 2500din., IC <3lt. y GC <5.5lt., tienen una asociación estadísticamente significativa con resultados perinatales adversos.

Palabras Clave: hemodinamia materna, resultado perinatal adverso, preeclampsia, diabetes gestacional, muerte perinatal.

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Discussion: Unlike what was reported, we established cut-off points to perform subgroups that demonstrate association with preeclampsia, gestational diabetes, adverse perinatal outcome and perinatal death.

Conclusions: IC<3lt obtained sensitivity of 78% and specificity of 66% to detect adverse perinatal results (OR 1.46), and OR 2.4 to develop gestational diabetes and 100% of Preeclampsia. RVP>1200din., IRVP>2500din., IC<3lt. and GC<5.5lt., have a statistically significant association with adverse perinatal results.

Keywords: maternal hemodynamics, adverse perinatal outcome, preeclampsia, gestational diabetes, perinatal death.

I. Introducción

La gestación normal representa un fenómeno de inmunomodulación local única, en el que existe una tolerancia natural entre dos tejidos antigénicamente dispares[1]. Este fenómeno de tolerancia inmunológica se produce básicamente a nivel local, en la interfaz uteroplacentaria y probablemente existen varios factores implicados[2], de estos, se incluye la implantación placentaria.

a) Preeclampsia y adaptación hemodinámica

La preeclampsia se denomina síndrome multisistémico de gravedad variable, que es específico

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del embarazo y se caracteriza por una reducción en la perfusión sistémica generada por el vasoespasmo y la activación de los sistemas de coagulación. Ocurre después de la semana 20 de embarazo, durante el parto o en las primeras 6 semanas posteriores.[3] Cuando se realiza la implantación, comienzan los cambios de la hemodinámica que se han descrito clínicamente en múltiples estudios. El flujo sanguíneo durante el embarazo y el gasto cardíaco comienzan a aumentar durante el primer trimestre en condiciones normales, probablemente debido a un aumento en la frecuencia cardíaca y el volumen sistólico, así como a una disminución en la viscosidad sanguínea y las acciones vasodilatadoras de las hormonas producidas por la unidad fetoplacentaria.[3,4]

El concepto actual supone que la implantación placentaria normal representa un estado fisiológico de inmunotolerancia basado, entre otros posibles factores aún no identificados, en una expresión antigénica especial y un equilibrio local de citocinas.[5,6] Esta aberrante inmunotolerancia finalmente se manifiesta en la preeclampsia, gestacional diabetes y algunos resultados perinatales adversos (Figura 1).

b) Predicción en resultados perinatales

Los resultados perinatales adversos son otro problema de salud que, en el último boletín emitido por la OMS, es un problema de salud que debe abordarse. Estudios recientes han investigado alteraciones placentarias que inducen apoptosis, alteraciones vasculares y daño endotelial, que a su vez causan morbilidad fetal[7]. Los avances científicos en los últimos 20 años han aumentado la esperanza de que muchas de las complicaciones del embarazo sean detectables desde al menos 12 semanas de gestation.[8]

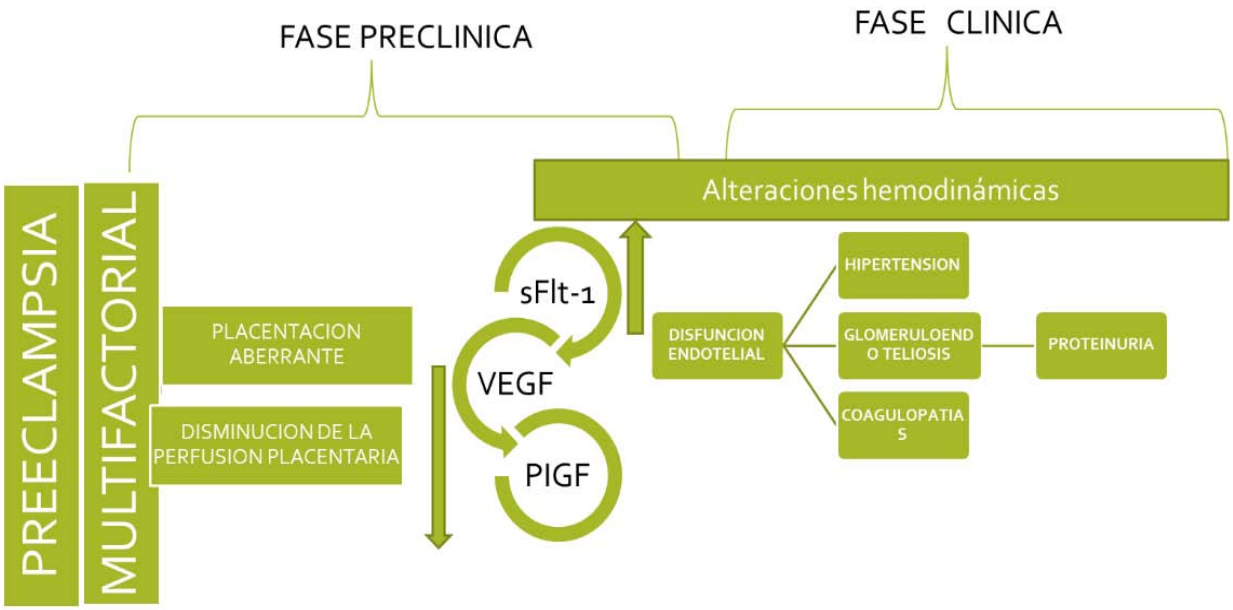


Figura 1: Fases preclínica y clínica de la Preeclampsia.

También es cada vez más evidente que una primera visita hospitalaria completa de 11 a 13 semanas que combina datos sobre características e historial maternos con los resultados de pruebas biofísicas y bioquímicas puede definir el riesgo específico del paciente para una amplia gama de complicaciones en el embarazo, incluido el aborto espontáneo y muerte fetal intrauterina, nacimiento prematuro, preeclampsia, diabetes gestacional, restricción del crecimiento fetal y macrosomía[9].

La evidencia actual sugiere que la fisiopatología de la restricción de crecimiento y la preeclampsia está íntimamente relacionada con el desequilibrio entre las proteínas angiogénicas y antiangiogénicas[10], que ha estado presentes desde el comienzo del embarazo y que es mensurable, con fines de cribado[11,12] desde la semana 11 a 14 de la gestación.

c) Monitor ultrasónico de gasto cardíaco (USCOM) en el embarazo

El USCOM es un monitor de rendimiento cardíaco ultrasónico que recientemente ha estado disponible en la práctica clínica y funciona midiendo la velocidad del flujo sanguíneo pulmonar o aórtico. Los algoritmos internos validados calculan el diámetro de la válvula aórtica y pulmonar en función de la altura y el peso del paciente. En manos de un usuario experimentado, el USCOM proporciona lecturas de gasto cardíaco que son del orden del 98% de precisión y se considera el método más preciso para medir el gasto cardíaco y las resistencias vasculares periféricas en la práctica clínica, muy superiores a este con respecto a otros métodos, como el cateterismo de la arteria pulmonar (Swan-Ganz) .[13]

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d) Antecedentes históricos sobre hemodinámica en el embarazo

La historia indica que el análisis del comportamiento del estado fetal, a pesar de que algunos aspectos anatómicos de la circulación fetal ya habían sido descritos por Galeno[14]. Satomura[15] en 1956, publicó las primeras aplicaciones de Doppler para el estudio de los flujos vasculares. Fitzgerald y Drumm[16] en 1977, realizaron por primera vez la evaluación del flujo umbilical mediante este procedimiento. En los últimos años, la aplicación del efecto Doppler, como complemento de la ecografía convencional, permite la evaluación de la hemodinámica fetal de forma no invasiva.

Otro estudio realizado en 2013 por Anne Marijin van der Graaf et al.[17] propone un dispositivo Doppler llamado "TheSphygmoCor" para monitorizar la onda de flujo de la arteria radial y USCOM, como métodos no invasivos fiables de evaluación hemodinámica durante el embarazo, fácil de usar, también encuentra una correlación de alteraciones en el gasto cardíaco y vascular periférico resistencia que en caso de placenta inadaptada se puede detectar con estos métodos desde el primer trimestre del embarazo.

Recientemente, Tiralongo et al[18] en febrero de 2015 describieron los efectos cardiovasculares del embarazo en el primer trimestre asociados con síndromes hipertensivos, estas evaluaciones fueron realizadas por USCOM, sus resultados muestran que la resistencia vascular periférica está elevada en el primer trimestre en pacientes normotensos y puede ser un marcador predictivo de preeclampsia. Otros métodos no invasivos como USCOM han demostrado el mismo patrón hemodinámico en la preeclampsia grave. Los resultados perinatales adversos son otro problema de salud que, en el último boletín emitido por la OMS, es un problema de salud que debe abordarse.[7]

La tecnología ha ayudado a comprender los mecanismos del desarrollo de los trastornos hipertensivos en el embarazo y el daño fetal, lo que lleva a una intentar predecir los eventos catastróficos que suceden en cada uno de ellos. Intentamos demostrar que la medición de variables hemodinámicas en mujeres embarazadas, a través del USCOM, puede ser una herramienta predictiva útil para resultados perinatales adversos. Por otro lado, el costo en comparación con otros marcadores es menor y su reproducibilidad es simple, sin embargo, como hemos visto en el fondo, se necesita más investigación para apoyar los resultados obtenidos y establecer puntos de corte en la población, que es por qué, el presente trabajo se desarrolla. Dentro de los nuevos objetivos del milenio, se pretende reducir la morbilidad y la mortalidad materna y fetal.

II. Material y Métodos

Se realizo un estudio de casos y controles anidados en una cohorte, el numero de la muestra se calculó basado en este diseño estadístico. Se incluyeron mujeres embarazadas que acudieron a la consulta prenatal en la Unidad de Ginecología y Obstetricia del Hospital General de México, de cualquier edad, que estaban embarazadas entre la semana 10-14 de gestación y que aceptaron ingresar al estudio mediante la firma del consentimiento informado fueron registrados. Distribuyó los grupos de acuerdo con los criterios de inclusión. Las mediciones del comportamiento hemodinámico se realizaron mediante USCOM [GC (gasto cardíaco), IC (índice cardíaco), RVP (resistencia vascular periférica) e IRVP (índice de resistencia vascular periférica)] en pacientes embarazadas en la semana 10-14, la técnica de medición fue como a continuación: Los pacientes fueron registrados con el número de archivo, se registraron el peso, la altura, la saturación.[10] El seguimiento posterior y el control prenatal se llevaron a cabo de acuerdo con las guías de práctica clínica correspondientes. Al final del embarazo, se evaluaron los resultados maternos y fetales.

Se estratificaron y clasificaron dichos resultados según el comportamiento hemodinámico. Al final del embarazo, la asociación entre los valores medidos con USCOM y el desarrollo de las variables independientes se analizó por medio de estadísticas descriptivas para la expresión de los resultados con la distribución de frecuencia: obtención de frecuencias absolutas (números de casos), las frecuencias relativas (porcentajes), las frecuencias ajustadas y acumuladas. Y estadísticas inferenciales o comparativas por Student's Xi2 o T dependiendo de la curva de distribución de frecuencia, así como al realizar tablas de contingencia que determinan la sensibilidad, especificidad y valores predictivos de la prueba, así como la regresión cuadrática lineal realizada con la versión estadística SPSS 22 (IBM, Armonk, NY, EE. UU.).

III. Resultados

El tamaño de muestra se completó en 93 pacientes de acuerdo con la metodología, se establecieron dos grupos: un grupo de bajo riesgo (control) y un grupo de alto riesgo (casos), la relación de casos y controles se estableció en 1:2 respectivamente, 62 pacientes se obtuvieron para el grupo de control o de bajo riesgo y 31 en el grupo de casos o de alto riesgo. Las estadísticas descriptivas para el grupo de bajo riesgo fueron: la edad media fue de 26,1 años, el índice de masa corporal (IMC) 26, el peso de 63,5 kg y la edad gestacional de 12,9 semanas. Para el grupo de alto riesgo, la edad fue de 28.5 años, índice de masa corporal de 26.1, peso de

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61.3 y edad gestacional de 12.4 semanas. La comparación de los promedios entre ambos grupos no presenta diferencias significativas, excepto en la edad gestacional. (Tabla 1) Al observar el resultado de la cohorte (n: 93) se observó el desarrollo de Diabetes en 23.7% (n: 22), Preeclampsia 6% (n: 6), el resultado perinatal adverso fue presentado en un porcentaje total de 35.5% (n: 33) y muerte perinatal en 7.5% (n: 7), pero sin diferencias significativas cuando se realiza Chi2 entre grupos de bajo y alto riesgo (tabla 2).

Tabla 1: Se demuestra homogeneidad en la caracterización mediante t de student entre el grupo de bajo y alto riesgo. Se observa que el patrón hemodinámico del GC, IC, RVP e IRVP no es diferente entre grupos lo cual sugiere que la alteración hemodinámica se debe a un factor intrínseco del embarazo.

	Grupo de bajo riesgo n 62/93	*Grupo de alto riesgo n 31/93*	*Total n: 93*	*Valor de P*
Edad	26.1 (26.1-27.8)	28.5 (26.3-30.7)	27 (14- 42)	0.102
IMC	26.0 (25.9-27.1)	26.1 (24.3-27.7)	26.14 (18.06 – 39.30)	0.930
Peso	63.5 (61.0-66.3)	61.3 (57.3-65.2)	63.01 (42.3 – 94.0)	0.346
EG	12.9 (12.6-13.1)	12.4 (12.1-12.6)	12.771 (11.0 – 14.2)	0.008*
TAM	77.7 (76.4-79.9)	82.2 (79.2-85.8)	79.62 (61.67 – 103.3)	0.010*
TAS	104.4 (102-107)	109.7 (105-113)	106 (80 – 130)	0.023*
TAD	64.4 (63.0-66.6)	68.5 (65.2-71.9)	66 (50 – 91)	0.023*
GC	4.6 (4.3-4.8)	4.4 (4.1-4.7)	4.5 (2.8 – 9.4)	0.516
IC	2.77 (2.6-2.9)	2. 70 (2.5-2.9)	2.7 (1.4 – 4.4)	0.638
IRVP	2380 (2244-2582)	2526 (2318-2720)	2446 (1298-5196)	0.301
RVP	1428 (1356-1534)	1528 (1403-1649)	1469 (742-2519)	0.204

Tabla 2: Estadístico Chi^2. Compara al grupo de bajo y alto riesgo con la presencia de Preeclampsia, diabetes gestacional, muerte perinatal y resultado perinatal adverso, sin diferencias significativas.

Desenlace	*Chi²*	*Valor de P*
Preeclampsia	0.00	1.000
Diabetes gestacional	0.74	0.442
Muerte perinatal	1.93	0.271
Resultado perinatal adverso	0.85	0.369

Se realizaron subgrupos comparativos para cada variable hemodinámica de acuerdo con los puntos de corte establecidos por las curvas ROC con mayor sensibilidad y especificidad para el desarrollo de variables independientes (figura 2 y tabla 3) en el caso del índice cardíaco en menor y mayor a 3 litros, establecer este punto de corte, se realizó una curva ROC que da una sensibilidad y especificidad para resultados adversos del 78% y 66% respectivamente, se observa que el valor de p al aplicar chi2 es significativo para la aparición de preeclampsia y el desarrollo de diabetes gestacional, cuando el índice cardíaco es menor a 3.

Área bajo la curva

Variable(s) de resultado de prueba	Área
GC	.591
IC	.630
IRVP	.412
RVP	.427

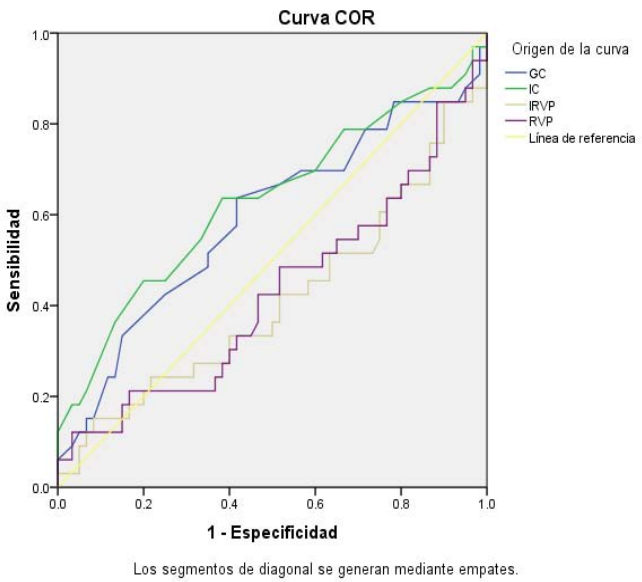


Figura 2: Curva ROC para las variables hemodinámicas respeto a resultados perinatales adversos. Esta arrojó una sensibilidad y especificidad de 78% y 66% respectivamente tomando como punto de corte IC con valor de 3 l/s.

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Tabla 3: Resultados de curva ROC respecto a sensibilidad y especificidad de puntos de corte para las variables independientes.

Punto de corte	*Preeclamsia*	*Diabetes gestacional*	*Muerte perinatal*	*Resultado perinatal adverso*
GC (5 Lt)	S: 83 E: 85	S: 81 E: 85	S: 85 E: 84	S: 84 E: 85
IC (3 Lt.)	S: 83 E: 70	S: 77 E: 69	S: 85 E: 69	S: 78 E: 66
IRVP (2500din)	S: 50 E: 36	S: 63 E: 63	S: 71 E: 36	S: 51 E: 73
RVP (1200din)	S: 83 E: 77	S: 72 E: 78	S: 85 E: 76	S: 78 E: 76

Si se establece en un valor inferior a 2,5, esto es significativo para el desarrollo de resultados perinatales adversos; de manera similar en la prueba de Moisés para la dirección de las distribuciones si hay significancia estadística para todas las variables (Tabla 4).

Tabla 4: Determinación de OR de variables independientes con la presencia de IC menor a 2.5 y 3 litros.

Variable	Grupos % <3: n 58 >3: n 35	OR	RR	Chi 2	Prueba de Moses de reacción extrema
Diabetes gestacional	<3: 81.8 >3: 18.2	0.287 (0.88-0.93)	2.4 (0.95-6.05)	**0.043***	0.000
Preeclampsia	<3: 100 >3: 0	---	---	**0.049***	0.000
Resultado perinatal adverso	>2.5: 16.1 <2.5: 19.4	**2.40** **(1.46-5.73)**	1.46 (0.96-2.22)	**0.046***	0.000
Muerte Perinatal	>2.5: 5.5 <2.5: 10.5	2.03 (0.42-9.68)	1.41 (0.59-3.37)	0.36	0.000

Con el punto de corte de la resistencia vascular sistémica en 1200 dinas, se determinaron la odds ratio (OR) y los riesgos relativos (RR), el grupo que presentó menos de 1200 dinas y el mayor de 1,200 dinas contra el desarrollo de diabetes gestacional (OR 0.7, RR 1.07), preeclampsia (OR 2.01, RR1.72), resultado perinatal adverso (OR 1.72, RR 1.49) y muerte perinatal (OR 2.27, RR 1.92); sin embargo, no se muestra que el valor p sea significativo. Cuando se encontraron OR sugestivos de riesgo, pero no significativos y observando la distribución porcentual por grupo, se decidió realizar una reacción extrema de Moses encontrando que las distribuciones de cada grupo mantienen un significado diferente, siendo estos con un valor p significativo (Tabla 5).

Tabla 5: Asociación de variables con la presencia de RVP >1200 dinas.

Variable	Grupos % <1200: n 26 >1200: n 67	OR	RR	Chi 2	Prueba de Moses de reacción extrema
Diabetes gestacional	<1200 d: 26.9 >1200 d: 22.4	0.78 (0.27-2.2)	1.07 (0.78-1.4)	0.64	0.000
Preeclampsia	<1200 d: 3.8 **>1200 d: 7.5**	2.01 (0.22-18.1)	1.72 (0.27-10.6)	0.52	0.000
Resultado perinatal adverso	<1200 d: 21.1 **>1200 d: 35.5**	1.72 (0.63-4.66)	1.49 (0.70-3.17)	0.28	0.000
Muerte Perinatal	<1200 d: 3.8 **>1200 d: 9**	2.27 (0.26-19.83)	1.92 (0.30-12.1)	0.44	0.000

Para dar mayor fuerza a los resultados previos, se realizó una regresión lineal en busca de asociación de resistencia vascular periférica (PVR) y gasto cardíaco (CG), la curva de mayor asociación resultó ser cuadrática, por lo que se realiza en presencia de preeclampsia. r2 = 0,857, p 0,008; desarrollar diabetes gestacional con un valor de r2 = 0.865, p 0.000; en presencia de resultado perinatal adverso con r2 = 0.803, p 0.000; y con muerte perinatal con r2 = 0.969, p 0.011). Respecto al índice cardíaco menor a 3 e índice de resistencia vascular periférica mayor a 2500 se encuentra una asociación mediante regresión cuadrática lineal de Preeclampsia r2 = 0.927 con valor de p 0.011, para la aparición de Diabetes gestacional r2

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= 0.908 con valor de p 0.000, asociado a un resultado perinatal adverso r2 = 0.806 con un valor de p 0.000, finalmente asociado con la muerte perinatal r2 = 0.993 y un valor de p 0.011.

La prueba t de Student se realizó para evaluar los resultados de recién nacidos vivos en términos de edad gestacional, Capurro, peso y altura contrastando por grupo de casos y controles, distribuyendo la población entre grupos mayores de 1200 dinas y menos de 1200 dinas con p-valores mayores que 0.05 (Tabla 6).

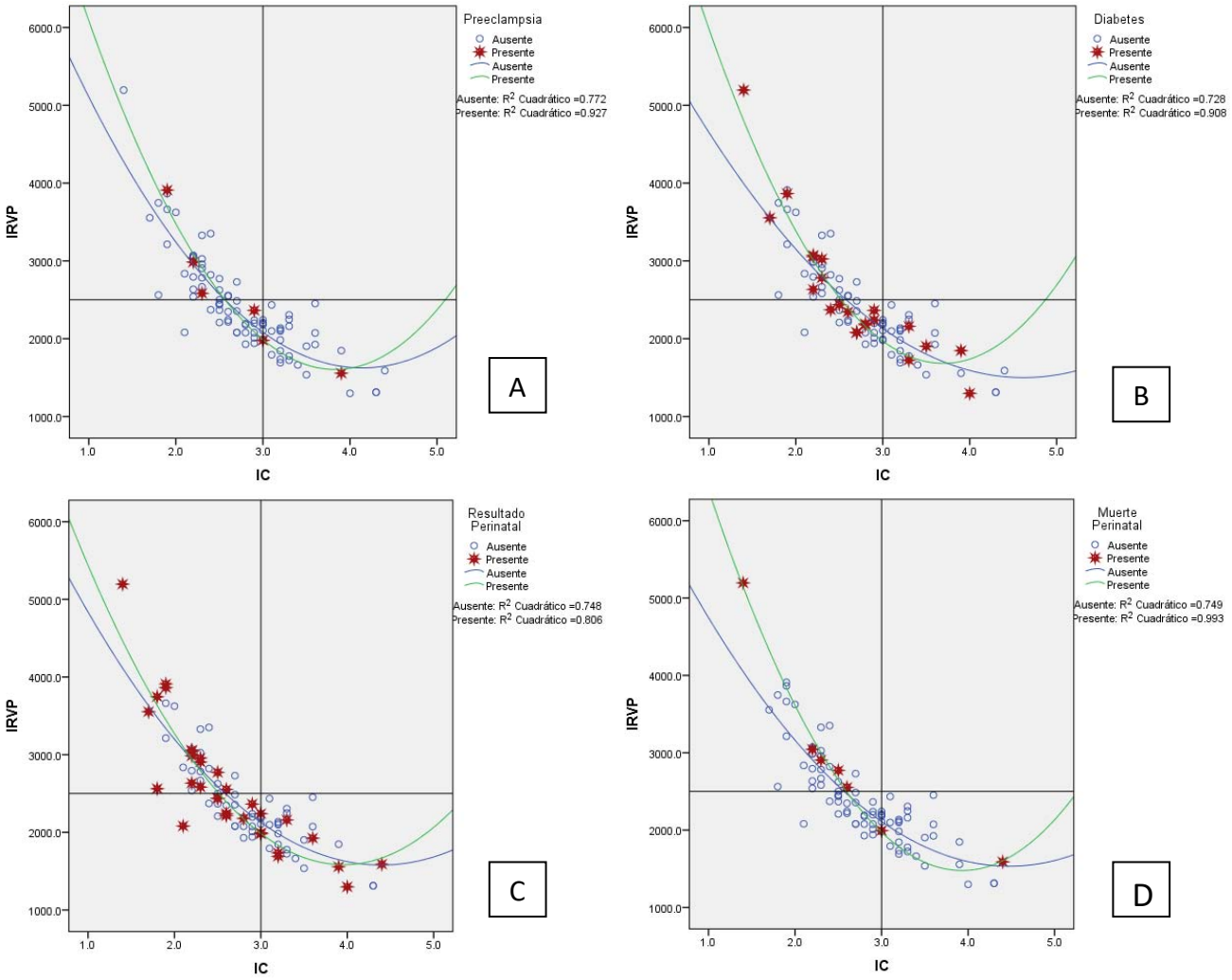


Figura 3: Regresión lineal cuadrática, asociación del índice de resistencias vasculares periféricas (IRVP) e índice cardiaco (IC) ante la presencia de: A) Presencia de preeclampsia (r^2 0.927, p 0.011). B) Diabetes gestacional (r^2 0.908, p 0.000). C) Resultado perinatal adverso (r^2 0.806, p 0.000). D) Muerte perinatal (r^2 0.993, p 0.011). Se representa además las medias que se tomaron como punto de corte tanto de IRVP e IC para cada grupo.

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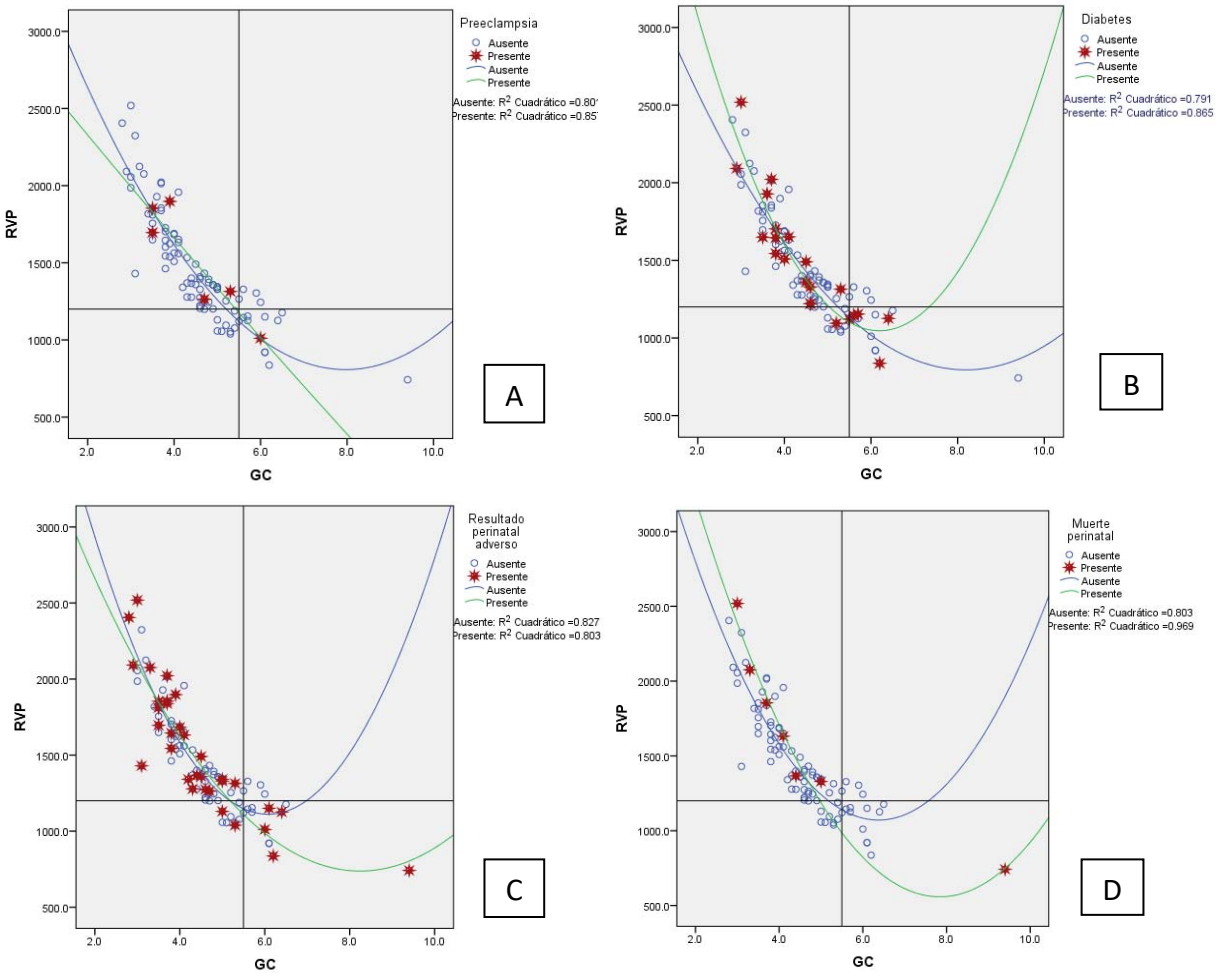


Figura 4: Regresión lineal cuadrática, asociación de las resistencias vasculares periféricas (RVP) y gasto cardiaco (GC) ante la presencia de: A) Presencia de preeclampsia (r^2 0.857, p 0.008). B) Diabetes gestacional (r^2 0.865, p 0.000). C) Resultado perinatal adverso (r^2 0.803, p 0.000). D) Muerte perinatal (r^2 0.969, p 0.011). Se representa además las medias que se tomaron como punto de corte tanto de RVP y GC para cada grupo.

Tabla 6: Diferencia de medias de los resultados neonatales en grupo de alto riesgo y bajo riesgo, y con menos de 1200 dinas y más de 1200 dinas en resistencias vasculares periféricas.

	Grupo Bajo Riesgo n: 62	Grupo Alto Riesgo n: 31	Significancia
Capurro	37.6	35.4	0199(-1.19-5.59)
Peso	2905	2732	0.278(-145.3-490.0)
Talla	48.8	48.7	0.832(-1.19-1.48)
Apgar 5´	8.5	7.5	0.12(-0.26-2.13)

	< 1200	>1200	Significancia
Capurro	37.4	36.89	0.721 (-2.3-3.45)
Peso	2867.3	2854	0.915(-235-262)
Talla	48.8	48.7	0.909(-1.2-1.4)
Apgar 5´	8.5	8.1	0.456(0.66-1.45)

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IV. Análisis y Discusión de Resultados

Se ha establecido que el aumento del 10% en los niveles de presión arterial iniciales conlleva el riesgo de desarrollar preeclampsia, restricción del crecimiento[20], muerte y diabetes gestacional;[21] nuestros resultados son similares a los reportados en la literatura. Sin embargo; al comparar las variables hemodinámicas, no se observaron diferencias significativas entre estos grupos, lo que sugiere que las alteraciones hemodinámicas pueden deberse a un trastorno intrínseco del embarazo que se suele descompensar durante el transcurso del mismo, esto explicaría por qué no todos los pacientes de alto riesgo desarrollan preeclampsia o resultados perinatales adversos asociados con insuficiencia placentaria. Existen varias publicaciones que muestran esta tendencia a la insuficiencia placentaria[22]. En contraste con lo que se informa, establecemos puntos de corte para realizar subgrupos que demuestran asociación con preeclampsia, diabetes gestacional, resultado perinatal adverso y muerte perinatal. Estos puntos de corte fueron: gasto cardíaco de 5,5 litros, índice cardíaco de 3 litros, resistencia vascular total de 1200 dinas e índice de resistencia vascular mayor de 2500 dinas, encontramos que existe una probabilidad de riesgo de desarrollar preeclampsia, resultado perinatal adverso y muerte perinatal. Como es el caso específico del índice cardíaco menor que 3, dado que en nuestra cohorte la probabilidad de desarrollar diabetes gestacional aumentó 2.4 (p 0.043), el riesgo de preeclampsia en este grupo fue del 100% con un valor de p 0.049. Si este punto de corte se reduce a 2,5 litros, se logra un riesgo de 1,46 la probabilidad de desarrollar algún resultado perinatal adverso. Para diferenciar la dirección de estos grupos como factores de riesgo, se aplicó la prueba de Moses de reacción extrema en la que se muestra que diferenciar los grupos de riesgos presenta diferentes significados. Este patrón de gasto cardíaco e índice disminuidos y resistencia vascular periférica elevada se ha observado en varias publicaciones asociadas principalmente con preeclampsia,[12,19,23] pero algunas descripciones de este patrón también se encuentran en el desarrollo de restricción del crecimiento[23] y muerte intrauterina o infertilidad temprana,[24] pero vale la pena mencionar que estas publicaciones solo mencionan la tendencia, en nuestro trabajo determinamos valores específicos para nuestra población dentro de las 10 a 14 semanas de gestación. Esta razón para identificar las asociaciones de nuestras variables dependientes con variables independientes y observamos una fuerte asociación con peso estadísticamente significativo para bajo gasto cardíaco de 5.5 con resistencia vascular periférica mayor de 1200 dinas e índice cardíaco bajo (menos de 3 litros) con índice de resistencia alto (más de 2500 dinas) en el desarrollo de diabetes gestacional, preeclampsia, resultado perinatal adverso (restricción del crecimiento intrauterino, prematurez, muerte embrionaria y fetal) y muerte perinatal, sin embargo, a diferencia de lo que se ha informado en la literatura[12,19] Los resultados de los nacidos vivos de esta cancha no mostraron diferencias significativas en términos de Capurro, Apgar, tamaño y peso, cabe mencionar que los fetos menores de 20 semanas fueron eliminados, por lo que estos resultados pueden estar sesgados.

V. Conclusión

Suponemos que la ausencia de diferencias hemodinámicas entre grupos de bajo y alto riesgo para desarrollar alteraciones como preeclampsia, diabetes gestacional, resultados perinatales y muerte perinatal han sido algo intrínseco al embarazo, que a su vez dependerá de la tolerabilidad fisiológica de cada mujer embarazada. El índice cardíaco inferior a 3 obtuvo una sensibilidad del 78% y especificidad del 66% para detectar resultados perinatales adversos con una probabilidad de 1,46 veces más de desarrollarlos. Con este valor hay una probabilidad 2.4 veces mayor de desarrollar diabetes gestacional y el 100% de la preeclampsia tuvo este valor entre las semanas 10 y 14. El patrón de resistencia vascular sistémica alta (mayor de 1200), alto índice de resistencia vascular (mayor a 2500), bajo índice cardíaco (menos de 3) y bajo gasto cardíaco (menos de 5.5), medido en la semana 10 a la semana 14, tienen una asociación estadísticamente significativa con preeclampsia, resultado perinatal adverso, diabetes gestacional y muerte perinatal.

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Conflicto De Intereses

Los autores se declaran sin conflicto de intereses.

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Infiltration of Leukocytes into the Human Ejaculate and its Association with Semen Quality and Oxidative Stress with Sperm Function, and Leukocytospermia Management

By Noureddine Louanjli, AyaAl-ibraheemi, Mustafa Zakaria, Abdelhafid Natiq, Romaissa Boutiche, Modou M. Mbaye & Mohamed Zarqaoui

Abstract- Leukocytes are white blood cells that are specialised in initiating an immune response against pathogens. There are several types of leukocytes in the human body with various functions; also, leukocytes can be found in different parts of the body, protecting against pathogens. In the male reproductive system, leukocytes can be detected through many methods, and it has been shown the effectiveness of those leukocytes in defending the reproductive system. Yet, the high level of leukocytes can generate reactive oxygen species that can harm the sperms. Moreover, a high level of leukocytes can lead to a condition called leukocytospermia, which can point to low fertilisation, pregnancy and embryo development rate. Accordingly, this article will discuss the potential harm of high leukocytes level, in addition to the management and treatment of leukocytospermia.

Keywords: leukocytes function and location, female reproductive tract, male reproductive tract, leucocytes and male fertility, management of leucocytospermia.

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Infiltration of Leukocytes into the Human Ejaculate and its Association with Semen Quality and Oxidative Stress with Sperm Function, and Leukocytospermia Management

Noureddine Louanjli [α], AyaAl-ibraheemi [σ], Mustafa Zakaria [ρ], Abdelhafid Natiq [ω], Romaissa Boutiche [¥], Modou M. Mbaye [§] & Mohamed Zarqaoui [χ]

Abstract- Leukocytes are white blood cells that are specialised in initiating an immune response against pathogens. There are several types of leukocytes in the human body with various functions; also, leukocytes can be found in different parts of the body, protecting against pathogens. In the male reproductive system, leukocytes can be detected through many methods, and it has been shown the effectiveness of those leukocytes in defending the reproductive system. Yet, the high level of leukocytes can generate reactive oxygen species that can harm the sperms. Moreover, a high level of leukocytes can lead to a condition called leukocytospermia, which can point to low fertilisation, pregnancy and embryo development rate. Accordingly, this article will discuss the potential harm of high leukocytes level, in addition to the management and treatment of leukocytospermia.

Keywords: leukocytes function and location, female reproductive tract, male reproductive tract, leucocytes and male fertility, management of leucocytospermia.

Abbreviations

In-vitro fertilization (IVF), White blood cell (WBC), Reactive oxygen species (ROS), Nonsteroidal anti-inflammatory drugs (NSAIDs), Sperm DNA fragmentation (SDF)

I. Introduction

a) Leukocytes function and location

Leukocytes are white blood cells, which are part of the immune system. They participate in powering inflammatory responses to any pathogens. Leukocytes are produced in the bone marrow, which is the manufacture of thousands of immune cells. Leukocytes production starts with pluripotent stem cells differentiation into various immune cells [1]. Leukocytes can be classified as granulocytes, including neutrophils, basophils, and eosinophils cells, agranulocytes that consist of lymphocytes and monocytes. Granulocytes leukocytes have granules (lysosomes) and special granules with unique substance to each cell's function. Therefore, granulocytes can be identified from each other by their nucleus morphology, their size, and their granules stain. On the other hand, agranulocytes don't have any granules and any specific substance [2]. Leukocytes blood circulating time is almost hours, which is considerably shorter for erythrocytes, and consequently, their appearance in the peripheral blood indicates their transition from their site of production to function place. However total white blood cell count (WBC) is a regularly evaluated value on the routine complete blood count is useless if differential counts have not been performed to help recognise the specific altered cell types in number by processes such as exercise or disease. Moreover, leukocytes can be separated in the spleen; therefore, their appearance in the peripheral blood can be primarily influenced by exercising, thus changing the cortisol and catecholamine profile [3]. Different types of Leukocytes have various functions in the body. For example,

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Neutrophils are responsible for pathogens defence, such as fungus and bacteria; they are released with early acute inflammation and makes up 60% of the leukocyte's cells. While Eosinphile acts in allergic reaction and parasitic invasions. Other leukocytes such as Basophile are also involved in an allergic reaction, plus histamine release. Most importantly, macrophage cells are responsible for pathogens phagocytosis *(Figure 1)*[4].

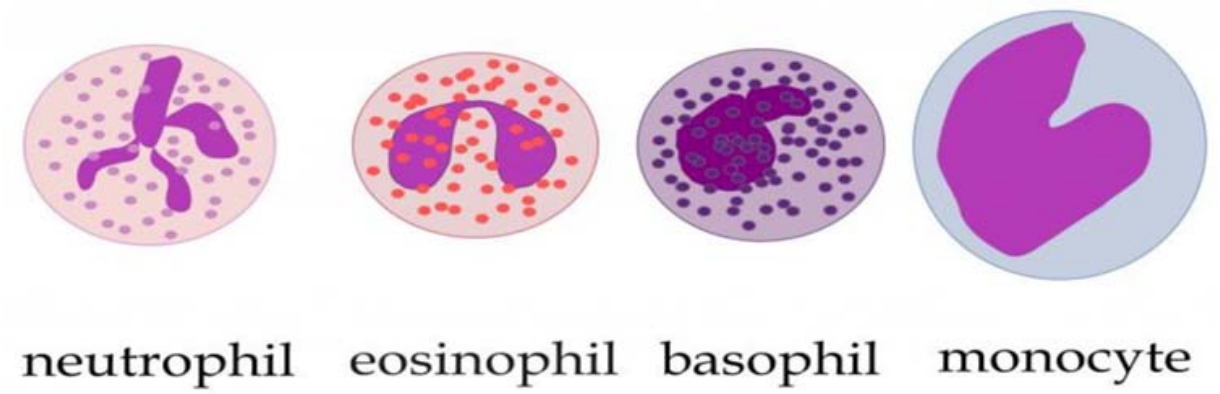


Figure 1: Different types of leukocytes in the human body [5].

b) Leukocytes in the Reproductive Tract

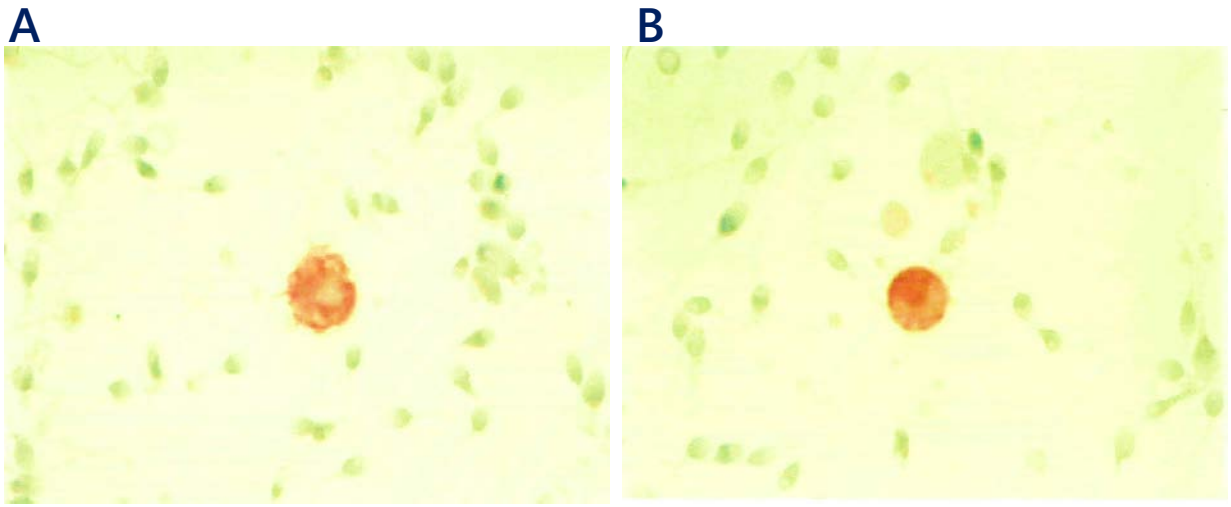
i. *Female reproductive tract*

Leukocytes can be found in the reproductive tract to perform fundamental functions. Immune mechanisms play essential functions in the cervix, uterus, fallopian tubes and ovary; throughout the reproductive tract, several cells and mediators' immune cells can be found. Reproduction disorder and infertility, such as pre-eclampsia, un-explained infertility, endometriosis, recurrent miscarriage, and disorganised fetal growth, can have a dysfunctional immune regulation. Through the female reproductive tract, the ovary also seems to be an essential immune-endocrine-reproductive interactions site. Moreover, leukocytes and their mediators, cytokines, are imperative components of normal physiological function, such as follicular development, ovulation and corpus luteum function[6]. Neutrophils and macrophages are the primary immune cells observed in the ovary, although mast cells, eosinophils and lymphocytes can also be found. Most neutrophils or macrophages are ejected from the granulosa layer by the basement membrane within theca and granulosa layers. A massive increase of leukocyte numbers in the ovary is associated with LH surge, particularly neutrophils, macrophages and mast cells [6].

ii. *Male reproductive tract*

As for the male reproductive system, leukocytes can be found in the semen, whose physiologic function is to eliminate abnormal germline from the ejaculate. During the male lifetime, most fertile and infertile men will have significant leukocytes in their seminal fluid [7]. Leukocytes normality in semen has been defined as I x 106 ml with values more; any higher number of leukocytes in the seminal fluid is considered leukocytospermic as identified by the World Health Organization. The exact origin of seminal leukocytes is still unknown; however, histological examinations have shown leukocyte populations in almost all male reproductive tract tissues [7]. Leukocytes can be found in different parts of the male reproductive; in the testes, male germ cells grow while separated from the immune system by the blood-testis barrier. Therefore, the male gamete continues to grow for a period of time in an immunologically privileged place. Yet, in the rete testes and epididymis, no such wall exists. The immunological and inflammatory responses can directly contact the millions of spermatozoa stored in this organ. The epididymis is an immunologically competent tissue that can evoke inflammatory reactions such as epididymitis infection [7]. Moreover, in normal fertile men, a vast amount of macrophages were identified within the seminiferous tubules in direct contact with the external layer of the tubule wall and surrounding the blood vessels in the interstitial [8]. Furthermore, in the rete testis of man, macrophages cells are mainly found in the connective tissue, where most of them expressed HLA DR antigens, showing their ability to start an immune response. However, it still not clear if these cells are phagocytic and antigen-presenting [8]. There is now solid experimental data which indicates that immunoregulation in the testicular and epididymal leukocytes perform a fundamental role, both systemically and locally, in the male tract. The immunoregulation mechanisms and the specific purpose of the leukocytes still need to be illustrated clearly. It is suggested that the macrophages of the testis and epididymis can limit antigen presentation by phagocytosis of spermatozoa with the consequent rapid loss of antigenicity; yet, macrophages primary function is antigen-presenting *(Figure 2)* [8].

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Some researchers have described a positive correlation between seminal leukocyte and semen quality as phagocytosis by leukocytes help to reduce abnormal spermatozoa from the semen. Furthermore, it has been shown that higher seminal leukocyte concentration can improve sperm motility [9]. As in Tomlinson et al., study, the results indicate high suggestive of a phagocytic mechanism for the elimination of morphologically abnormal spermatozoa in the ejaculate[10]. However, in teratozoospermia patients, both the leukocyte total and the number of functional phagocytes were significantly lower, proposing that in teratozoospermia patients, the mechanism of abnormal spermatozoa elimination was inadequate. In addition, there was an influential association with the total of both macrophages and HLA-DR expression in head defects sperms. This indicates that abnormal sperms can be detected via antigenic determinants around the head region of the spermatozoon[10].

c) Leucocytes and male fertility

As mentioned earlier leucocytes is common to be found the human seminal fluid, yet several studies reported negative effect of leucocytes on sperms parameters, fertility and semen quality. Male infertility has been found to be link with an increase in the rate of leucocytes in semen beginning from subclinical infections of the epididymis, the prostate, or and the seminal vesicles, which also can influence fertilization, implementation and embryo development[11]. Leukocytospermia-induced sperm defects is a possible outcome of the high levels of reactive oxygen species (ROS) derived by leukocyte and inflammatory mediators. High-level ROS production has generally been identified as the mechanism by which pathogens and leukocytes are producing harm to the sperms through triggering lipid peroxidation and damaging mitochondrial activity. Also, it is well known that spermatozoa are very sensitive to ROS and oxidative stress due to their unique plasma membrane and cytoplasm, which contains a high level of polyunsaturated fatty acids[12]. ROS is recognised in the male genital tract to generate immature spermatozoa and leukocytes (chiefly neutrophils and macrophages). The invade of bacteria triggers tissue site defences of the host in unique or non-specific immunity way in all the tract including testis, epididymis, prostate gland and seminal vesicles. Spermatozoa in seminal plasma are in contact with leukocytes for a comparatively short period of time, particularly from the point of ejaculation till the male germ cells reach the cervix[9].The mechanism of ROS action starts with ROS production by the leukocytes to fight infections by attacking pathogens through stimulating G6PDH activity, allowing high NADPH levels production. NADPH oxidase then reduces NADPH electron to transform oxygen to superoxide anion *(Figure 3)* [9].

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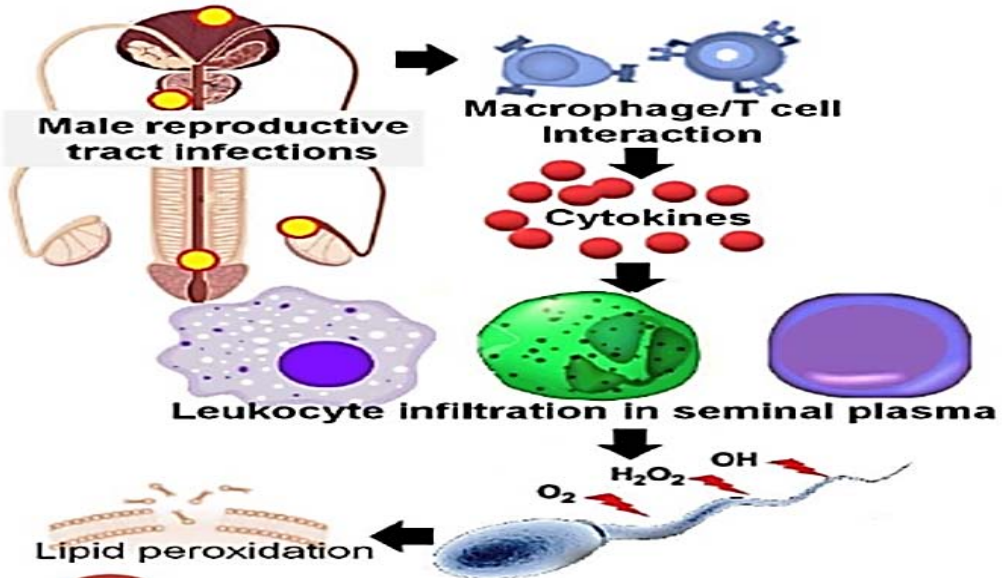


Figure 3: Mechanisms of male reproductive tract infection. The above diagram illustrates how the leukocytes cell invade and fight the pathogens in the male reproductive tract [9].

Furthermore, ROS can harm the sperm plasma membrane through lipid peroxidation, which has a remarkably high quantity of polyunsaturated fatty acids; consequently, it is prone to oxidative damage. Moreover, ROS has been correlated to an increase in sperm DNA fragmentation (SDF). Thus, DNA-damaged spermatozoa can be found in all-male reproductive tract sites, reflecting that the ox-oxidative damage can happen in testis and epididymis, and the ejaculate[12]. Even if the male accessory sex glands are infected, sperm function, including the DNA, can be influenced through the influence of ROS generated by stimulated leukocytes as they stimulate apoptosis in mature human spermatozoa Bacteria can too cause spermatozoa apoptosis. Sperm DNA injury can influence early post-implantation embryo development and therefore reduce the fertility and pregnancy rate[12]. Free radicals can immediately harm sperm DNA by attacking the purine and pyrimidine bases. Most sperm genome is connected to central nucleoproteins that defend them from free radical attack; therefore, ROS produce injury to single and double-strand DNA breaks, cross-links, and chromosomal rearrangements [13]. an infertile male usually has insufficient protamination, allowing their sperm DNA more exposed to ROS damage. Also, another spermatic DNA damage mechanism is free radical-initiated apoptosis, pointing to DNA destruction. Sperm repair mechanisms in haploid spermatozoa are required to provide chromatin rearrangement; however, spermatozoa have an insufficient capacity to repair DNA and can barely be performed through specific stages of spermatogenesis. Interactions of sperm with an oocyte can permit some DNA repair, affecting fertilisation and possible pregnancy *(Figure 4)* [13].

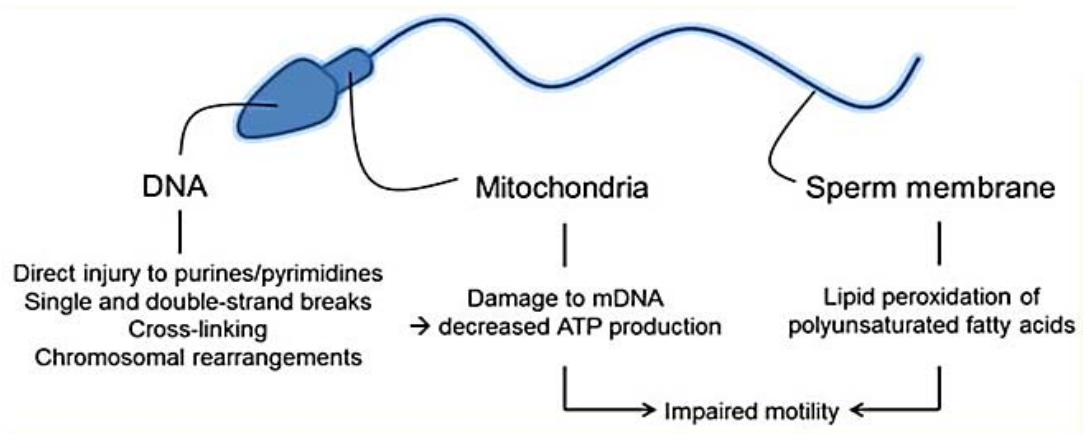


Figure 4: Pathological effects of ROS on spermatogenesis and function[13].

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ROS level can be measured through direct or indirect assays. Direct assays measure the oxidation levels of the sperm cell membrane. Indirect assays measure the damaging impacts of oxidative stress, like sperm DNA damage levels. The chemiluminescence technique is a direct assay that is usually applied to measure seminal ROS [14].Several pieces of research look into the effects of abnormal leucocytes on sperm parameters and fertility outcomes. Effects on semen parameters In Yilmaz et al., study, they tried to determine the impacts of leucocytospermia on semen parameters and ICSI result in infertile patients. The median leucocyte concentration was 2.68 million/ml in the leucocytospermic group. Semen forward progressive motility rates were (1.5% vs 3%), and sperm concentrations (12 vs 29 million/ml). Sperm concentrations were significantly lower in the leucocytospermic patients. The total motility rates were similar between the groups (56% vs 58%). However, after semen preparation, there was no difference between progressive forwarding motility (16% vs 19%) and total motility rates (85% vs 79%) within the groups [15].In addition, the effects of leucocytes on ICSI was determined by fertilization rate and embryo development. The detection of leucocytes reduced fertilization and embryo development rates. Fertilization rates (82% vs 87%) and embryo development rates (79% vs 86%) in the leucocytospermic group were significantly lower than those of the non-leucocytospermic group. Still no significant difference in embryo quality between the leucocytospermic group and the non-leucocytospermic group (88% and 92% for good quality embryos and 11% and 3% for deficient embryos respectively) [15]. They also reported that low fertilization rates seem to be reasonable as leucocytospermic samples produced oxidative stress enough to damage DNA in sperms, and the rate of spermatozoa with fragmented DNA is proposed to have a negative association with fertilization rates in IVF [15]. Moreover, the presence of leucocytes cells negatively influenced both the fertilization and the pregnancy rate in IVF and embryo transfer. Both the number of fertilized oocytes and the pregnancies rate were decreased in the presence of more than 4 x 10' of leucocytes cells/ml in semen samples. However, the differences were not statistically significant. Also, the fertilization rate was decreased significantly ($p<O.O5$) in the presence of >8% of leucocytes cells. Besides, it was reported that that the detection of any seminal leukocytes was related to oxidative stress; thus, it not possible to establish the minimum level of WBCs correlated with oxidative stress. In addition, there was a significant negative correlation between oxidative stress and sperm concentration, motility, and sperm morphology, indicating the influential association of ROS with poor semen quality [16]. Also, in SHARMA et al., study, ROS was detected in artificial conditions while the seminal plasma washed away[16]. This method, consequently, indicates the generation of ROS by granulocytes and macrophages only in the absence of seminal plasma. Such leukocyte-derived ROS can be free to harm and attack spermatozoa while they are washed free of seminal plasma through the swim-up method[16]. Moreover, to assess the outcome of assisted reproductive treatment, it has been reported that fertile male had a higher mean number of round cells in their semen than infertility patients; also, pregnancy percentage increased from 12.4% with no round cell's sperms to 18.0% and 16.8% with rising concentrations of round cells. In addition, there was a significant rise in the percentage of pregnancy loss, from 13.2% for the group with no leukocytopenia to 36.4% when leukocytes were higher than 106/ml, and followed by a reduction in the delivery rate from 83.7% to 63.6% [17]. Accordingly, a better pregnancy rate was obtained, with significantly better motility, vitality, and sperm morphology. The study was concluded by that, leukospermia does not impact the pregnancy rate, yet, it is linked with increased pregnancy loss, as in infertility patients [17]. Furthermore, a significant number of asymptomatic infertile men were diagnosed with leukocytospermia; in addition, leukocytospermia was negatively associated with sperm morphology. Therefore, solvent leukocyte cells can influence fertility through reducing sperm motility and fertilizing ability[18]. The results of Arata et al., show that leukocytes in the semen of infertile men are correlated with a significant decrease in sperm concentrations, percent motile sperm, sperm membrane integrity, and sperm morphology, implying that leukocyte cells can impair male fertility[18]. On the other hand, several researchers have been performed to assess the impact of leucocytes on the sperm parameters, which include motility, morphology and numbers of sperms. One study illustrates an increase in normal morphology and progressive motility in semen samples with leukocyte concentrations ranging from 0-1.0 $\times$ 106/ml. However, there was a reduction in each parameter at a leukocyte threshold >1 $\times$ 106/ml. Moreover, all sperms types had damages rose progressively with rising leukocyte counts[19]. Moreover, in RJ et al., study they examined the semen profile, as they found that the presence of various leukocyte types in the human ejaculate was significantly linked with exfoliated germ cells[20]. There were few exfoliated germ cells detected; however, there was a significant correlation with the size of the different leukocyte subpopulations in the human ejaculate. The presence of several leukocyte species was also correlated with sperms concentration, especially with type B cells or monocytes/macrophages. Additionally, sperm function was also observed, where a significant impact of leukocyte contamination on the capacity of the washed sperm preparations for sperm-oocyte fusion

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was detected. Accordingly, when those leukocytes were recognised in these washed sperm preparations, sperm-oocyte fusion did not happen due to the high rate of ROS activation.

d) Management of leucocytospermia

There has been a considerable debate regarding the threshold point of the leukocyte's percentage in the seminal fluid; some have found this value too low, others too high depending on their methods applying. The WHO Laboratory guidelines suggest that a single peroxidase test be performed in 1 + 9-diluted should be applied for semen to assess leukocytes to examine human semen[21]. The appearance of one activated leukocyte per 20000 sperm can result in a considerable number of ROS; therefore, even a deficient amount of leukocytes in the sperm suspension can impact the integrity of sperm and, accordingly, the result of assisted reproduction treatment. Thus, having a precise and very sensitive technique to detect seminal leukocyte is of paramount importance[22]. In addition to the Peroxidase rest, swim-up and density gradient centrifugation are still the most well-known techniques for separating functionally healthy spermatozoa. Swim-up can give a sperm suspension with a lower level of leukocyte contamination than that obtained after density-gradient centrifugation [22]. The most common management protocol for leuctocytospermia is the elimination of infection and protection against ROS generated within cellular mitochondria due to inflammation. Below is a flow chart that illustrates the clinical management of leuctocytospermia *(Figure 5)* [23].

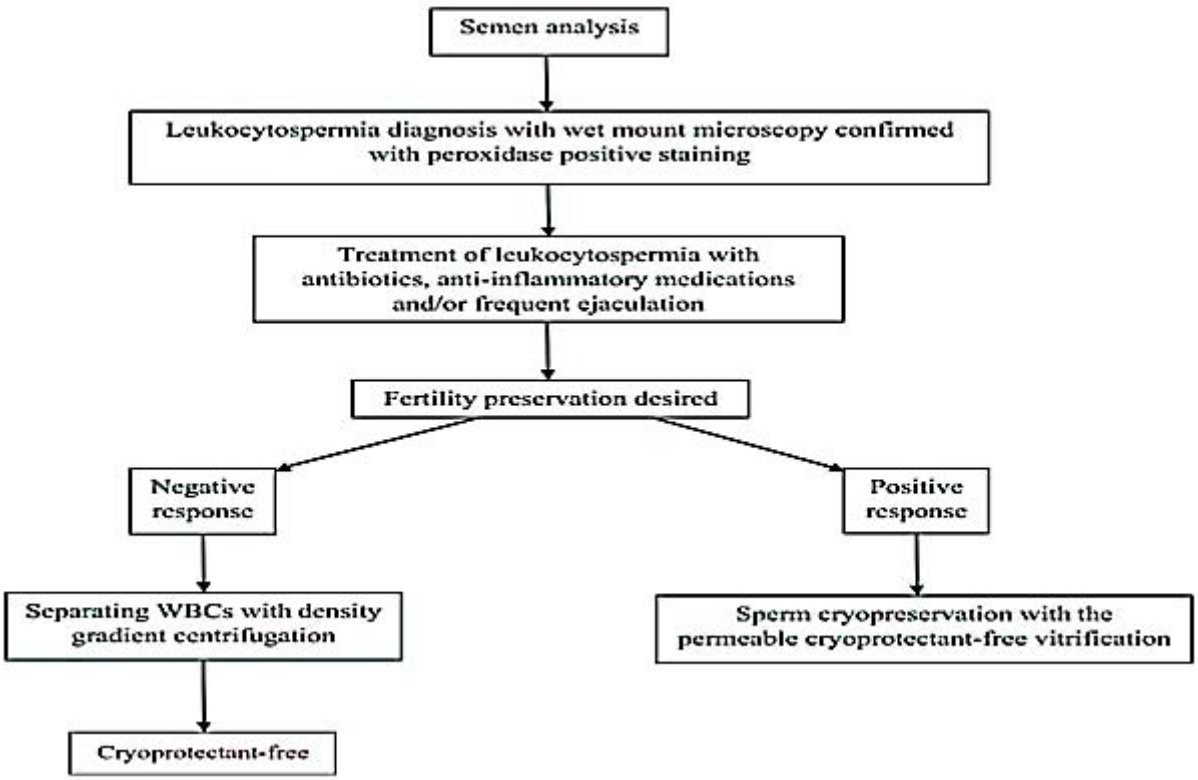


Figure 4: Management of semen samples obtained from leukocytospermic infertile males [23].

Several meta-analyses confirmed that applying broad-spectrum antibiotics to treat patients with leukocytospermia may enhance sperm concentration, motility, and morphology. Yet, these researches did not report any influence on pregnancy or adverse effects [24]. Jung et al., 2016, reported a noticeable decrease in leukocytospermia percentage in the treated group than the untreated group, in addition to a significant reduction in the number of seminal bacteria in the treatment group[24]. Usually, there is no clear protocol for the treatment of leukocytospermia; however, antibiotics can advance the overall quality of spermatozoa, but there is no evidence of increased pregnancy rates after antibiotic treatment of the male partner. The various medication has been used in the treatment for leukocytospermia[23]. For instance, ketotifen, an antihistamine-like drug, enhanced sperm motility and morphology in patients with leukocytospermia. Antioxidants have been applied to decrease the generation of ROS by seminal leukocytes. Nonsteroidal anti-inflammatory drugs (NSAIDs) were observed to improve sperm count, motility, and morphology in asthenoteratozoospermia men with leukocytospermia. In conclusion, these researches show the conflict in the debate about the management and treatment of leukocytospermia[23].

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II. Conclusion

In conclusion, leukocytes infiltration into the human ejaculate is normal and can be detected in the healthy fertile male semen sample; however, if a high level of leukocytes is found in the seminal fluid, it can indicate a male reproductive tract infection that can potentially influence male fertility. Although leukocytes role is debatable, some researchers have suggested that seminal leukocytes can't be just a response to infection; however, it works to attack abnormal germ cells and can perform some positive role in surveilling and phagocytosing of abnormal and dead spermatozoa. Yet, it has been shown in this research paper that a high number of leukocytes in the seminal fluid can lead to leukocytospermia, which can impact male fertility, embryo development and pregnancy rate. Suppose proper sperm separation methods have been used to separate leukocytes from health sperms before assisted reproduction. In that case, the generated spermatozoa will be completely functional and able to fertilize the oocyte and develop an embryo.

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Hospital based Prospective Study of Thrombocytopenia in Pregnancy

By Dr. Swati Motilal Maraskolhe & Dr. Ashok Ramchandra Anand

Abstract- *Background:* Thrombocytopenia is the second most common hematologic abnormality after anemia during pregnancy and is usually a benign condition. Thrombocytopenia affects 7% to 10% of all pregnant women. All pregnant women with platelet counts less than 100000/mm3 require careful hematological and obstetric consultation to rule out other more serious disorders.

Objectives: To study the various etiological factors associated the effect and outcome of the mother and neonates born, to study the Management in pregnancy.

Methods: The study was conducted in this tertiary institute over a period of two years and three months. 130 pregnant patients with a platelet count of or less than 100000/mL were included. The course of pregnancy was studied and the investigation profile and maternal and fetal outcome was monitored.

Keywords: *thrombocytopenia, pregnancy.*

GJMR-E Classification: *NLMC Code: WH 315*



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Hospital based Prospective Study of Thrombocytopenia in Pregnancy

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Abstract- Background: Thrombocytopenia is the second most common hematologic abnormality after anemia during pregnancy and is usually a benign condition. Thrombocytopenia affects 7% to 10% of all pregnant women. All pregnant women with platelet counts less than 100000/mm3 require careful hematological and obstetric consultation to rule out other more serious disorders.

Objectives: To study the various etiological factors associated the effect and outcome of the mother and neonates born, to study the Management in pregnancy.

Methods: The study was conducted in this tertiary institute over a period of two years and three months. 130 pregnant patients with a platelet count of or less than 100000/mL were included. The course of pregnancy was studied and the investigation profile and maternal and fetal outcome was monitored.

Result: Out of 130 cases 107 cases (17.69%) had severe thrombocytopenia and 23 cases (82.3%) had moderate thrombocytopenia. Total incidence of thrombocytopenia in prganncy is 2.8 %.In this study 42.3% cases were primigravidas, 58 % cases were multigravida. In this study gestational thrombocytopenia was the most common etiological factor with 42% cases followed by other infectious diseases, 1.5% for pregnancy induced hypertension and for eclampsia, 25.5% cases for HELLP syndrome. 3.07% cases of severe thrombocytopenia had deranged liver function tests and 21.5% cases of moderate thrombocytopenia had deranged liver function tests. In this study out of the total 4.8% acute febrile illness cases 1.5% had P. vivax Malaria. And Among the 6 cases of dengue in this study, 0.7 % were IgM positive, 3.8% were NS1Ag positive. Most of the 63.7% cases were of ≥36 weeks of gestation. In this study out of 130 cases there were 10 (7.69%) neonatal deaths.

Conclusion: Conclusion from this study is the incidence of thrombocytopenia during pregnancy is quite uncommon that is 2.8% and if present with thrombocytopenia then it is considered as an emergency for an obstetrician mostly during labor or whenever she having bleeding Fetal outcome in pregnant patients with thrombocytopenia was favourable; it was dependent on the gestation of delivery.

Keywords: thrombocytopenia, pregnancy.

I. Introduction

Platelet abnormalities may precede pregnancy, developed during pregnancy coincidentally or be induced by pregnancy. Pregnancy is associated with physiological and pathological changes in platelet numbers and function which can be of clinical concern. Inherited defects in platelet function and number may also manifest during pregnancy with the risk of bleeding dependent on the underlying problem. Thrombocytopenia affects 7% to 10% of all pregnant women and other than anemia is the most common hematologic disorder in pregnancy.[2]

Thrombocytopenia in pregnancy may occur secondary to a variety of causes ranging from benign disorders such as gestational thrombocytopenia to syndromes associated with significant morbidity such as eclampsia, HELLP, ITP, TTP-HUS. Other causes of thrombocytopenia in pregnancy are rare such as Type II von Wiillebrand Disease (vWD), and disseminated intravascular coagulation.

Among the all causes most common cause is Gestational Thrombocytopenia, Which is 75 % occure mostly in third trimester and is through to be predominantly due to hemodilution. All pregnant women with platelet counts less than 100000/mL require careful hematological and obstetric consultation to rule out other more serious disorders.

To reduce the platelet disorder related complications during pregnancy, there should be stratification done regarding the predictors, frequency and their effects on the foetus.

In this study we study the various etiological factors associated, the effect and outcome of the mother and neonates borne to study the Management in pregnancy.

a) Aims and objectives of the study

1. To study the various etiological factors associated with thrombocytopenia in pregnancy
2. To study the number and percentage of cases of moderate and severe thrombocytopenia in pregnancy.
3. To study the different diseases in which thrombocytopenia manifests in ANC patients.
4. To study the effect and outcome of the mother and neonates borne to them.
5. To study the management of cases of thrombocytopenia in pregnancy.

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6. To study the morbidity and mortality associated with thrombocytopenia in pregnancy.

II. Methods

Study-Hospital based prospective study

Inclusion criteria

1. Pregnant patients with 2nd and 3rd trimester with low platelet count.
2. Platelet count equal to or below 100000 per micro-liter were included in the study in Pregnant women.

Exclusion Criteria– 1) Patients on steroid, NSAIDS therapy or who underwent for splenomegaly.

The study was conducted in the tertiary institute over a period of two years and three months, from. 130 pregnant patients with a platelet count of or less than 100000/mL were included in the study group. Patients with 2nd And 3rd trimester of pregnancy were included. On admission a thorough history was taken and a detailed clinical examination was carried out. All the patients were subjected to biochemical investigations, special investigations and ultrasonography.

Patients were grouped into 2 categories- one with moderate thrombocytopenia (platelet count >50000 or less than or equal to 100000/ml and one with severe thrombocytopenia (platelet count equal to or less than 50000/ml).

The course of pregnancy was studied and the investigation profile was monitored. The obstetric outcome was noted. The entire hospital stay course was noted. Final outcome of all cases and complications if any was studied.

Table no. 1: Distribution according to parity

Parity	No.	Percentage
Primigravida	55	42.3
Multigravida	75	58
Total	130	100

III. Result

The total number of deliveries in our institute over the period from Jan 2017 to July 2018 was 4669. Out of deliveries, there were 130 cases of Thrombocytopenia. Thus the incidence of Thrombocytopenia in the present study is 2.8%.

In this study 42.3% cases were primigravidas, 58 % cases were multigravida.

Table no. 2: Distribution of case according to weeks of gestation

Weeks of gestation	No.	Percentage
26-30	14	10.7
31-35	34	26.1
36-41	82	63.07
Total	100	100%

In this study 10.7% cases were of 26-30 weeks of gestation, 26.1% cases were of 31-35 weeks of gestation, 63.7% cases were of ≥36 weeks of gestation.

Table no. 3: Distribution of cases according to OBSTETRIC HIGH RISK CONDITION

Obstetric high risk condition	No. of patients(50)	Percentage (%)
HELLP	33	25.53
Severe PIH	2	1.54
DIC	10	7.6
Antepartum hemorrhage	5	3.8

In this study most common high risk condition is HELLP among 33 patient and percentage 25.53%

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Table no. 4: Distribution of case according to Etiology

Etiology	No.	Percentage
Gestational Thrombocytopenia	55	42%
Dengue	8	6.6%
HEELP	33	25.5%
DIC	10	7.6%
ART Induced	1	0.7%
Heparin Induced	1	0.7%
Idiopathic	5	3.8%
Pancytopenia	2	1.5
Severe PIH	2	1.5
APH	5	3.8
Acute Febrile Illness	6	4.8%
P.Vivax	2	1.5%
Total-	130	100%

In this study gestational thrombocytopenia was the most common etiological factor with 42% cases followed by 1.5% for malaria followed by 6.6% for dengue, 1.5% for pregnancy induced hypertension and for eclampsia, 25.5% cases for HELLP syndrome. 3.07% cases of severe thrombocytopenia had deranged liver function tests and 21.5% cases of moderate thrombocytopenia had deranged liver function tests.

In this study out of the total 4.8% Acute febrile illness cases, 1.5% had P. vivax Malaria. And Among the 6 cases of dengue in this study, 0.7 % were IgM positive, 3.8% were NS1Ag positive.

Table no. 5: Distribution of case according to Classification of Thrombocytopenia

PLT Count	No.	Percentage
Moderate (>50,000)	107	82.3
Severe (<50000)	23	17.69
Total	130	100%

Out of the 130 cases, 107 cases (82.3%) had moderate thrombocytopenia and 23 cases (17.69%) had severe thrombocytopenia.

Vaginal delivery was the most common mode of delivery seen in 87% of the patients. 13.07% of the cases had LSCS, with 5 Still birth with 24 are FTND with episiotomy, 50 are FTND with intact perineum, and 34 are PTVGD.

Table no. 6: Distribution according to mode of delivery

Mode of delivery		No. of patients (N = 60)		Percentage (%)
Vaginal	FTND with episiotomy	24	113	87
	FTND with intact perineum	50		
	PTVGD	34		
	Still birth	5		
LSCS		17		13.07

Vaginal delivery was the most common mode of delivery seen in 87% of the patients. 13.07% of the cases had LSCS, with 5 Still birth with 24 are FTND with episiotomy, 50 are FTND with intact perineum, and 34 are PTVGD.

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Table no.7: Distribution of case according to Neonatal Outcome

Outcome	No. of patients (N = 130)	Percentage (%)
Baby with mother	99	76.15
Baby in NICU	26	20
Still birth	5	3.86

Above data states that most common neonatal outcome was baby with mother in 76.15% of the patients

Table no. 8: Distribution of cases according to other associated medical disorder

Medical disorder	No.(25)	Percentage (%)
Dengue	8	6.6
ART induced	1	0.7
Heparin induced	1	0.7
Idiopathic	5	3.8
Pancytopenia	2	1.5
Acute febrile illness	6	4.8
P.Vivax	2	1.5

Analysis of Platelet Transfusion

No. of cases requiring platelet transfusion (All cases) Antenatal & Postnatal	69
Mean +/- SD	4.16+/- 890
Median	5.130
Minimum	2
Maximum	132

As per this data, 53.07% of the patients had required platelet transfusion followed by 22.30% had required blood transfusion other 10 % need conservative treatment.

In this study 7.2% cases were of 19-20 years. of Age group, 44.1% cases were of 21-25 years of Age group. 27.4% cases were of 26-30 years of Age group.21.3% cases were of 31-40 years of age group.

This analysis reveals that, 14.61% of the cases were registered in Antenatal clinic followed by 78.46% of the patients came as referrals from other hospitals and 6.9 % of the cases were unregistered.

This data reveals that, 1.53% of the cases had 1 antenatal.

Visits followed by 14.61% of the patients had 2-4 antenatal visits and 6.8 % of the patients had 5-6 antenatal visits and 0.76 %of the patient had >6 visit.

In this study 1.5 % cases had deranged renal function tests. 98.46 % cases had renal function tests within normal limit. 1.5 % cases of moderate thrombocytopenia had deranged RFTs.

In this study 24.6 % cases had deranged liver function tests.75.4 % cases had liver function tests within normal limit. 21.5% cases of moderate thrombocytopenia had deranged LFTs.

As per this data, 5.38 % of the cases had Previous 1 LSCS followed by 2.3% of the cases had IUGR with with Fetoplacental Insufficiency and of Postdatism with thick MSAF.

As per this data, 39.23% of the babies were in the range of <1.5 followed by 31.53% of the babies were in the range of 2.1 – 2.5kg.

This data reveals that 7.61% of the patients had Low birth weight with respiratory distress was the commonest indication for admission of the NICU.

This data indicates that, Postnatal course was uneventful in 96.9 % of the patients.

As per this data, 2.30 % of the cases were admitted for Critical monitoring followed by 1.53% of the patient's was admitted for Ventilator Support.

As per this data, 2.30 % were admitted in the CCU for < 2 days.

Respiratory distress was the most common complication seen in 3.8% of the babies.

As per this data, 83.07% of the patients had duration of hospital stay < 10 days followed by 16.15% of the patients had hospital stay 11 – 20 days. The reason for prolonged stay was to monitor vital parameters, to look for signs and symptoms of bleeding and hypertension, to look for growth of baby.

The neonatal mortality with Severe birth asphyxia was 3.9% and with Cardiorespiratory arrest was 2.30% with the perinatal mortality rate was 8.5%.

The most common cause of stillbirth was prematurity. followed by 22.30% had required blood transfusion other 10 % need conservative treatment.

This data reveals that 88.28% of the babies had Apgar score in the range of 7 to 9.

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IV. Discussion

In this prospective study of all pregnant patients with thrombocytopenia with platelet count less than or equal to one lakh per mL were included.

The present study was aimed at investigating thrombocytopenia during pregnancy.

Their detailed history, examination findings, investigations were noted. Course of pregnancy was followed up and the maternal, obstetric and fetal outcome was studied.

The results of the study were then compared with the available literature and the following points were noted.

The total number of deliveries in our institute over the period from Jan 2017 to Aug 2018 was 4669. Out of deliveries, there were 130 cases of Thrombocytopenia. Thus the incidence of Thrombocytopenia in the present study is 2.8%.

From the above studies our study and Zahida Parveen Brohi[etall] shows similar findings of Incidence among the patient.

Age

In our study, most of the patients (n=60) i.e. 44.1% cases were of 21-25 yrs. of Age group with mean age of 30.7 ± 2.08 years in the study group.

Out of 130 patient total 14.61% of the cases were registered in Antenatal clinic followed by 78.46% of the patients came as referrals from other hospitals and 6.9 % of the cases were unregistered.14.61 % had 2-4 antenatal OPD visit and 6.9 % had no visit.

In this study 42.3% cases were primigravidas, 58 % cases were multigravida. most of the studies shows similar findings that most patient reported are primigravida.

In this study 26.1% cases were of 31-35 weeks of gestation with mean gestational age 34 +/- 5

Similar findings consistent with the study conducted by Michal Parnas[etall] 2005[1]<36 weeks– 25.6%,

In this study, 63.7% cases were of ≥36 weeks of gestation. The study conducted by Michal Parnas[etall] 2005 [1] observed that 37-39 weeks – 46.2% which shows opposite findings to our study.

In our study gestational thrombocytopenia (42%) was the most common etiological factor with 42% cases followed by 1.5% for malaria followed by 6.6% for dengue, 1.5% for pregnancy induced hypertension and for eclampsia, 25.5% cases for HELLP syndrome.

Michal Parnas[etall 20051] Observed that the main causes of thrombocytopenia were gestational thrombocytopenia 118 patient (GT) (59.3%),22 immune thrombocytopenic purpura (ITP) (11.05%), 20 with severe pre- eeclampsia (10.05%), and 24 with HELLP (Hemolysis, elevated liver enzymes and low platelet count) syndrome (12.06%).10 with DIC, 1 with TTP, 6.2% with APH.

In our study vaginal delivery was the most common mode of delivery seen in 87% of the patients. 13.07% of the cases had LSCS, with 5 Still birth with 24 are FTND with episiotomy, 50 are FTND with intact perineum, and 34 are PTVGD.

Michal Parnas[1etall] 2005 conclude that most common mode is Vaginal delivery. and LSCS is done only in case of any obstetric emergency.

Michal Parnas[1etall 2005] observed that most of the patient had vaginal deliveries 64 % and Cesarean section -36.2% preterm deliveries with higher rates of labor induction.

In our study the neonatal mortality with severe birth asphyxia was 3.9% and with Cardiorespiratory arrest was 2.30% with the perinatal mortality rate was 8.5 %. The most common cause of stillbirth was prematurity.

50 patients (38.46%) had preterm deliveries out of which 60 patients (56.07%) belonged to the severe thrombocytopenia group. This was due to the associated obstetric and medical complications that indicate preterm delivery.

10 patients (7.68%) had neonatal deaths (NNDs) as opposed to the study of *Parnas et al. in 2006*[1] in which 2.5% patients had NNDs. Out of that 2 patients (1.53%) belonged to the severe thrombocytopenia group. The association of NNDs with severe thrombocytopenia was not statistically significant and in the moderate thrombocytopenia group there were 6.15 % neonatal deaths.

Similar findings also reported in the study conducted by *Kasturi V. Donimath[etall]* in 2014-2015. [2]

According to Kasturi V. Donimath[2 etall] Prospective observational study was done during November 2014 to June 2015.Out of 100 cases 56% had thrombocytopenia. There was very high significant relationship between the degree of thrombocytopenia with the severity of the PIH (at p <0.001). 12% of the fetuses had IUD, 10% had IUGR, 4% died after birth and 2% had severe birth asphyxia.

In our study Out of the 130 cases, 107 cases (82.3%) had moderate thrombocytopenia and 23 cases (17.7%) had severe thrombocytopenia.

In the present study, Postnatal course was uneventful in 96.9 % of the patients. peurperal complications were seen in 3.07% patients. 4 patient were shifted to CCU (3.07% of cases) I/V/O the severe thrombocytopenia group with HELLP with DIC with severe anemia.

As per this data, 53.07% of the patients had required platelet transfusion followed by 22.30% had required blood transfusion other 10 % need conservative treatment.

As per this data, 2.30 % of the cases were admitted for Critical monitoring followed by 1.53% of the patient's was admitted for Ventilator Support.

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V. Conclusion

Conclusion from this study is the incidence of thrombocytopenia during pregnancy is quite uncommon that is 2.8% and if present with thrombocytopenia then it is considered as an emergency for an obstetrician mostly during labor or whenever she having bleeding .There are decreased in platelets count at different stages of pregnancy, most low platelet counts observed in the pregnant patients are due to normal physiologic changes and various pathological changes also.

This Study conclude that, Thrombocytopenia in pregnancy may occur secondary to a variety of causes. Most of these cases occur during specific periods of gestation. Out of the etiological factors most common cause of thrombocytopenia in pregnancy is gestational thrombocytopenia with the rate of 42%.

Early diagnosis and management play a key role in decreasing the adverse outcome by sunderstanding the auto-pathology. Treatment of thrombocytopenia depends upon the severity and condition of the patients.

The above observations show that failure can occur at any time during pregnancy or in the puerperium. Hence, constant vigilance and multidisciplinary approach. is required throughout antenatal, intrapartum and post-partum period.

Vaginal delivery is safer and caesarean section should be reserved only for Obstetric indications with access to intensive care units.

In my study emergency LSCS was done in fetal jeopardy and resulted favourable outcome.

Need of platelet transfusion depends on severity and the type of platelet disorder that patient have.

Cases of ITP is also observed which is diagnosed as an diagnosis of an exclusion and treated with Corticosteroids it is the first line of therapy for thrombocytopenia usually prednisone drug is used.

Patients with gestational thrombocytopenia and ITP have better maternal and perinatal outcomes as compared to preeclampsia and HELLP syndrome, which are associated with adverse feto-maternal outcome.

Fetal outcome in pregnant patients with thrombocytopenia was favourable; it was dependent on the gestation of delivery.

Prematurity and its complications with a rate of 7.61% were with most common associated with thrombocytopenia in pregnant patients.

Acknowledgment

I would like to express my special thanks of gratitude to my teacher Dr. Ashok Ramchandra Anand who gave me the wonderful opportunity to do this thesis project on the topic of hospital based prospective study of thrombocytopenia in pregnancy and I came to know and learn many new things for this I am really thankful to them.

Bibilography

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Use of Intravenous Ferric Carboxymaltose: A Revolutionary Approach for Iron Deficiency Anaemia in Antenatal Women

By Dr. Renu Gupta, Dr. Pavika Lal, Dr. Shaily Agarwal & Dr. Anita Gond

Introduction- Anaemia still has been prevailing as a significant global public health problem especially in low to middle economic countries, responsible for 40% of maternal deaths and out of which it accounts for 25% among direct cause. Besides maternal mortality it also causes increased perinatal morbidity and mortality although it is a major preventable cause of unfavourable perinatal and maternal outcome. There are various national programmes undertaken by Government of India catering to anaemia especially for pregnant population which has largely emphasised the oral iron supplementation but still the picture is gloomy and we have to go a long way. Prevalence of Iron deficiency anaemia (IDA) in pregnancy in India ranges from 23.6%-61.4%[1].

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Use of Intravenous Ferric Carboxymaltose: A Revolutionary Approach for Iron Deficiency Anaemia in Antenatal Women

Dr. Renu Gupta [α], Dr. Pavika Lal [σ], Dr. Shaily Agarwal [ρ] & Dr. Anita Gond [ω]

I. Introduction

Anaemia still has been prevailing as a significant global public health problem especially in low to middle economic countries, responsible for 40% of maternal deaths and out of which it accounts for 25% among direct cause. Besides maternal mortality it also causes increased perinatal morbidity and mortality although it is a major preventable cause of unfavourable perinatal and maternal outcome· There are various national programmes undertaken by Government of India catering to anaemia especially for pregnant population which has largely emphasised the oral iron supplementation but still the picture is gloomy and we have to go a long way. Prevalence of Iron deficiency anaemia (IDA) in pregnancy in India ranges from 23.6%-61.4%[1].

Different forms of oral iron preparations are available widely claiming the increased absorption rate with decreased side effect and have established to be a preferred route of administration for mild to moderate anaemia among pregnant population, but all has their own limitations like gastrointestinal side effects. Apart from oral preparation, parenteraliron sucrose therapy is an upcoming effective alternative but the main disadvantage of intravenous (IV) iron sucrose is that it cannot be administered at a higher dose because of the risk of toxicity, thus requiring frequent visits to the hospital[2]. Intravenous ferric carboxymaltose (FCM) have been developed recently; its properties like near neutral pH, physiological osmolarity and increased bioavailability permit the administration of large doses (15 mg/kg; maximum of 1000 mg/infusion) in a single and rapid session (15-minute infusion) without the requirement of a test dose [3]. It has a very low immunogenic potential and therefore not predisposed to anaphylactic reaction. Therefore, we undertook this study with the aim to compare the efficacy and tolerability of intravenous ferric carboxymaltose with oral iron therapy in pregnant population.

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II. Materials and Methods

This study was conducted in the department of obstetrics and gynaecology at Upper India Sugar Exchange Maternity Hospital, G.S.V.M. Medical College, Kanpur over a period from January 2019 to July 2020 after approval from ethical committee G.S.V.M Medical College Kanpur.

Study subjects: All antenatal patients, with hemoglobin range between 7-10.9 g/dl irrespective of parity.

Type of Study– Prospective interventional randomized clinical study.

Inclusion Criteria:

Patients willing to participate and follow up.

- Antenatal patients with a period of gestation 16-32 weeks.
- Haemoglobin level between 7-10.9 g/dl.
- Serum ferritin <30 mcg/L (Only for therapeutic group).
- Patients with known nutritional anaemia.

Exclusion Criteria:

- Pregnancy <16 weeks and after > 32 weeks period of gestation.
- Hemoglobin<7 gm/dl or >11 gm/dl.
- Intolerance to oral iron preparations
- Recent history of blood transfusion.
- History of any disease associated with iron overload disease like thalassemia, haemoglobinopathies like sickle cell anaemia.
- Multiple pregnancy.
- Hypersensitivity to iron preparations.
- History of antepartum haemorrhage.
- Known case of inflammatory bowel diseases.
- Serious medical condition like chronic kidney disease, severe cardiovascular diseases, hepatic diseases.
- Known case of hepatitis B, hepatitis C and HIV

III. Methodology

After written and informed consent of patients were enrolled in the study according to inclusion criteria. Sahli's method was used to know the baseline hemoglobin.

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Total 235 pregnant women were included in the study, who were divided into 2 groups according to degree of anaemia.

1. Preventive Group (9 – 10.9g/dl)
2. Therapeutic Group (7 – 9g/dl)

Further these groups were divided into two subgroups IA, IB, IIA, IIB. Number of patients in these groups were [IA (n=60), IB(n=55), IIA(n=65), IIB(n=55)].

- Group I: Preventive Group

IA were treated with tablets of ferrous ascorbate once a day containing 100mg elemental iron as well as 5 mg of folic acid with tablet vitamin C 500 mg.

IB were treated with intravenous ferric corboxymaltose 1000 mg single dose.

- Group II: Therapeutic Group:

IIA were treated with ferrous ascorbate 200mg elemental iron twice a day containing folic acid with tablet vitamin C 500mg.

IIB were treated with intravenous ferric carboxymaltose according to the calculated dose.

Iron Dose calculation: The total dose required for Hb restoration and repletion of iron stores was calculated by following Ganzoni formulae.

Total Iron deficit (mg) = Body weight in Kg x (target hemoglobin – actual hemoglobin) gm/dl x 2.4 + 1000 mg for iron storage

Ferric Carboxymaltose was administered only by I.V. drip infusion – maximum single dose of 500-1000 mg (20 ml) diluted in 100 ml sterile 0.9% NaCl solution over 15 minutes not more than once a week.

The patients were asked to follow up after 1 week, 3 weeks, 6 weeks and then till delivery.

1. Day 0: The blood samples were taken for the following investigations (Hb, MCV, MCH, MCHC and serum ferritin level, peripheral blood picture, reticulocyte count) before starting medication to know the baseline values.
2. 1 weeks: to assess the reticulocyte count.
3. 3 weeks: to assess the Hb, MCV, MCH, MCHC levels.
4. 6 weeks: to assess the Hb, MCV, MCH, MCHC & Serum ferritin levels.
5. Followed till delivery: to assess maternal & fetal outcome.

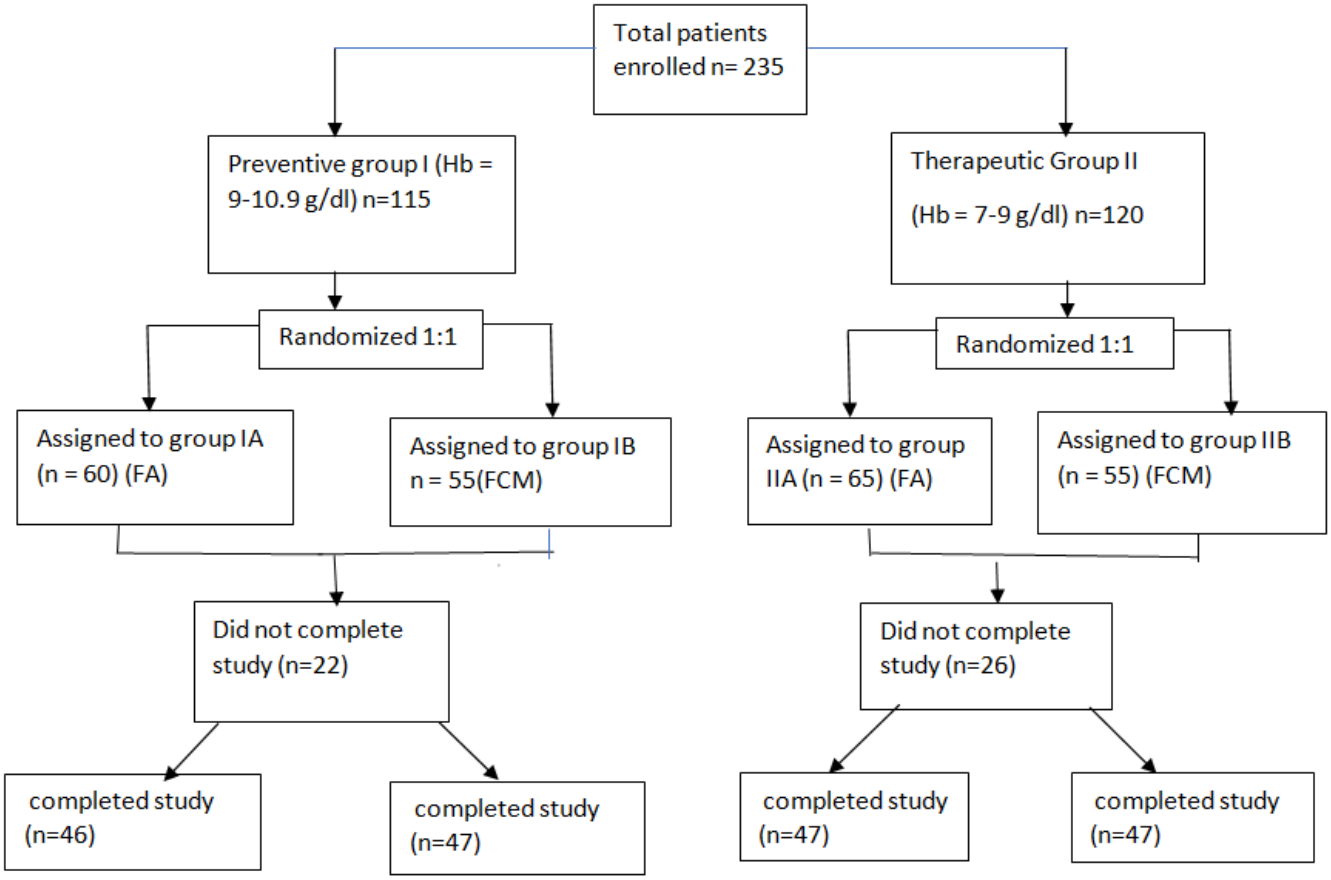
During each follow up visit, they were subjected to general examination and obstetrical examination. The patients were explained to record and observe the adverse effects and instructed to report immediately if serious adverse drug reaction occurs. Any adverse event like metallic taste, nausea, vomiting, dyspepsia, diarrhoea and constipation were recorded on the case record form in every follow up. Compliance was checked by verbal enquiry and verified by asking blackening of stools and staining of tongue.

IV. Statistical Analysis

Statistical analysis was done to analyse the difference in all the hematological parameters among the groups using percentages and chi-square test for categorical variables.

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Flowchart Representing the No. of Patients Enrolled During Study



V. Results

Majority of patients had mean age of 27.59±3.08 years in all groups. Mean age of gestation was 21.65±3.83 week, 47.33% were primigravida and 53.71% were multigravida, 56.42% belonged to rural, 17% were illiterate and 18.76% had primary level of education in our study. All groups were comparable in terms of sociodemographic and general characteristics of study populations.

Table 1: Comparison of Two Subgroups among Preventive Group

Variables	IA(Mean±SD)	IB(Mean±SD))	p-value
Baseline hemoglobin(g/dl)	9.59±0.51	9.68±0.53	<0.0001
Hemoglobin at 34-37 wk	12.20±0.45	12.70±0.58	<0.0001
Hemoglobin(g/dl) rise at 34-37wk	2.71±0.39	3.06±0.53	<0.0001
Baseline serum ferritin	39.01±9.0	42.42±12.06	<0.0001
Serum ferritin rise at 6 weeks	17.30±5.89	85.17±15.86	<0.0001

Mean reticulocyte count in patients of group IA was 1.10±0.30and of group IB was 1.04±0.22 after 1week post treatment, which was significantly higher in latter group (1.40 versus 1.80 g/dl; p<0.0001). Mean rise in Hb was 2.71±0.39 g/dl in group IA and 3.06±0.53g/dl in group IB. Thus, statistically the difference was highly significant (p<0.0001) (Table 1)

Table 2: Comparison of Two Subgroups among Therapeutic Groups.

Variable	IA(Mean±SD)	IIB(Mean±SD)	P-VALUE
Baseline hemoglobin	8.22±0.52	7.97±0.59	<0.0001
Hb (rise at 3 week)	0.89±0.36	2.24±0.58	<0.0001
Hb (rise at 6 week)	2.06±0.53	3.79±0.68	<0.0001
Baseline serum ferritin	20.09±4.22	18.17±4.27	<0.0001
Ferritn (rise at 6 week)	19.64±8.10	87.94±14.14	<0.0001

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Mean reticulocyte count of group IIA was 0.96±0.28% and that's of group IIB was 0.87±0.21% which was comparable before the intervention. At 1week post treatment, rise was higher in group IIB as compared to group IIA. Mean rise in reticulocyte count was 0.31±0.17 % in group IIA and 0.99±0.28 % in group IIB which was statistically highly significant (p<0.0001).

It was found that the mean rise in Hb and serum ferritin were higher in ferric carboxymaltose group as compare to ferrous ascorbate which was statistically highly significant (p<0.0001).

Table 3: Comparison of Other Parameters among Therapeutic Groups

Variables	IIA(Mean±SD)	IIB(Mean±SD)	P-VALUE
Baseline MCV	75.17±3.76	75.70±4.57	<0.0001
MCV (rise at 6 week)	7.62±2.62	11.60±2.89	<0.0001
Baseline MCH	26.34±1.54	26.22±1.54	<0.0001
MCH (rise at 6 weeks)	3.68±1.83	7.25±2.04	<0.0001
Baseline MCHC	28.39±1.97	28.37±2.07	<0.0001
MCHC (rise at 6 weeks)	3.99±1.53	6.73±1.45	<0.0001

Mean rise in mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC) was higher in ferric carboxymaltose group (IIB) as compared to oral ferrous ascorbate group (IIA) which was significant (TABLE 3).

Table 4: Comparison of Side Effects of FCM & Ferrous Ascorbate

	Ferrous ascorbate (IA+IIA)		Ferric carboxymaltose (IB+IIB)		P-VALUE
	n = 93	%	n = 94	%	
Gastrointestinal symptoms	45	48.38	1	1.06	<0.05
Hypersensitivity	00	00	00	00	-
Headache	00	00	1	1.06	-
Heartburn	2	2.15	00	00	-
Palpitations	00	00	1	1.06	
Total	47	50.6	3	2.7	-

Mild side effects were observed in 2.7% patients in FCM groups, while it was observed that 50.6% of patients in oral ferrous ascorbate group had significant side effects. No major adverse effects were noted making both the iron preparations safe in pregnancy (Table 4).

VI. Discussion

Iron deficiency anaemia is one of the most important causes of maternal and neonatal morbidity and mortality in developing world, so it should be corrected in all pregnant women to decrease its adverse related outcome. The aim of our study was to compare the efficacy, safety, tolerability and feto-maternal outcome of intravenous ferric carboxymaltose with oral ferrous ascorbate in pregnant women having mild to moderate iron deficiency anaemia. In our study, we found that for both preventive and therapeutic groups mean rise in haemoglobin at 6weeks post treatment was significantly higher in intravenous FCM group as compared to oral iron. *Bhargava and Maheshwari et al*[4], *Deeba et al* [5] studied that rise in haemoglobin was higher in intravenous group as compared to oral iron group. *Myers et al*[6] studied that ferric carboxymaltose group had the meanrise in hemoglobin was higher as compared to iron dextran after 6 weeks. *Onken et al* [7] study in antenatal patients, showed significant rise in mean hemoglobin in intravenous ferric carboxymaltose group as compared to oral iron.

In our study, there was a significant rise in serum ferritin levels after 6 weeks in preventive and therapeutic groups which was higher in intravenous FCM as compared to oral ferrous ascorbate which was highly significant. *Deeba et al* studied showed similar results as rise in serum ferritin after 6 weeks in ferrous ascorbate and *Mishra V et al* [8] found that mean serum ferritin risehigher in ferric carboxymaltose group.

Mean rise in MCV, MCH, MCHC in therapeutic group at 6 weekswere higher in intravenous FCM as compare to oral ferrous ascorbate groups and was highly significant. *Ambily J et al* [9] results were comparable with our study.

Fetomaternal outcomes were found better in intravenous FCM as compared to oral ferrous ascorbate but was not significant. Needs of blood transfusion and postpartum haemorrhage reduced in FCM group. *Anouk pel etal*[10] had done retrospective study and concluded that ferric carboxymaltose had slight less complications rate.

Gastrointestinal complications were more in oral ferrous ascorbate and which was nil in intravenous ferric carboxymaltose. There were no anaphylactic reactions reported with doses of intravenous ferric carboxymaltose. Side effects with oral ferrous ascorbate

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were more as compared to intravenous ferric carboxymaltose. *Iftikar et al* [11] *and Onken et al* [12] proved that ferric carboxymaltose was well tolerated and showed better compliance than oral iron. *Froessler et al*[13] also reported minimal side effects with intravenous ferric carboxymaltose.

VII. Conclusion

We deduced that all haematological parameters (Hb, reticulocyte count, mean rise in hemoglobin at 3 and 6 weeks and serum ferritin level) were significantly increased in intravenousferric carboxymaltose group as compared to oral iron group. Although various oral iron preparations are mainstay of treatment of anaemia in pregnancy claiming higher absorption as well as bioavailability, but in current scenario, injection ferric carboxymaltose seems superior to oral iron therapy as a definite treatment of iron deficiency anaemia in pregnancy in both second and third trimester of pregnancy.

Based on the observations of our study it is thus worthy to say that Ferric carboxymaltose, due to its high efficacy, tolerability and safety profile can revolutionize the management of iron deficiency anaemia in pregnancy. Therefore, it must be used as a first line drug for decreasing the high incidence and burden of the iron deficiency especially in our health set up. Therapy contributing to be the maternal morbidity and mortality as well in cutting down the economic burden on the health system of our country.

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

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Acknowledgments

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

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

Manuscript Style Instruction (Optional)

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

Structure and Format of Manuscript

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

A research paper must include:

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

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

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

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

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



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Format Structure

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

All manuscripts submitted to Global Journals should include:

Title

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

Author details

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

Abstract

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

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

Keywords

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

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

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

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

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

Numerical Methods

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

Abbreviations

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

Formulas and equations

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

Tables, Figures, and Figure Legends

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

Figures

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

Preparation of Eletronic Figures for Publication

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

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

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Tips for writing a good quality Medical Research Paper

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Informal Guidelines of Research Paper Writing

Key points to remember:

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

Final points:

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

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

The discussion section:

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

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

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- Submitting a manuscript with pages out of sequence.
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- Keep paying attention to the topic of the paper.
- Use paragraphs to split each significant point (excluding the abstract).
- Align the primary line of each section.
- Present your points in sound order.
- Use present tense to report well-accepted matters.
- Use past tense to describe specific results.
- Do not use familiar wording; don't address the reviewer directly. Don't use slang or superlatives.
- Avoid use of extra pictures—include only those figures essential to presenting results.

Title page:

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

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

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

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

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

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

Approach:

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

Introduction:

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

The following approach can create a valuable beginning:

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

Approach:

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

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

Procedures (methods and materials):

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

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

Materials:

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

Methods:

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

Approach:

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

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

What to keep away from:

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



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Results:

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

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

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

Content:

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

What to stay away from:

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

Approach:

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

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

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

Figures and tables:

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

Discussion:

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

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

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

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

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

Approach:

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

Describe generally acknowledged facts and main beliefs in present tense.

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Introduction	Containing all background details with clear goal and appropriate details, flow specification, no grammar and spelling mistake, well organized sentence and paragraph, reference cited	Unclear and confusing data, appropriate format, grammar and spelling errors with unorganized matter	Out of place depth and content, hazy format
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References	Complete and correct format, well organized	Beside the point, Incomplete	Wrong format and structuring

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