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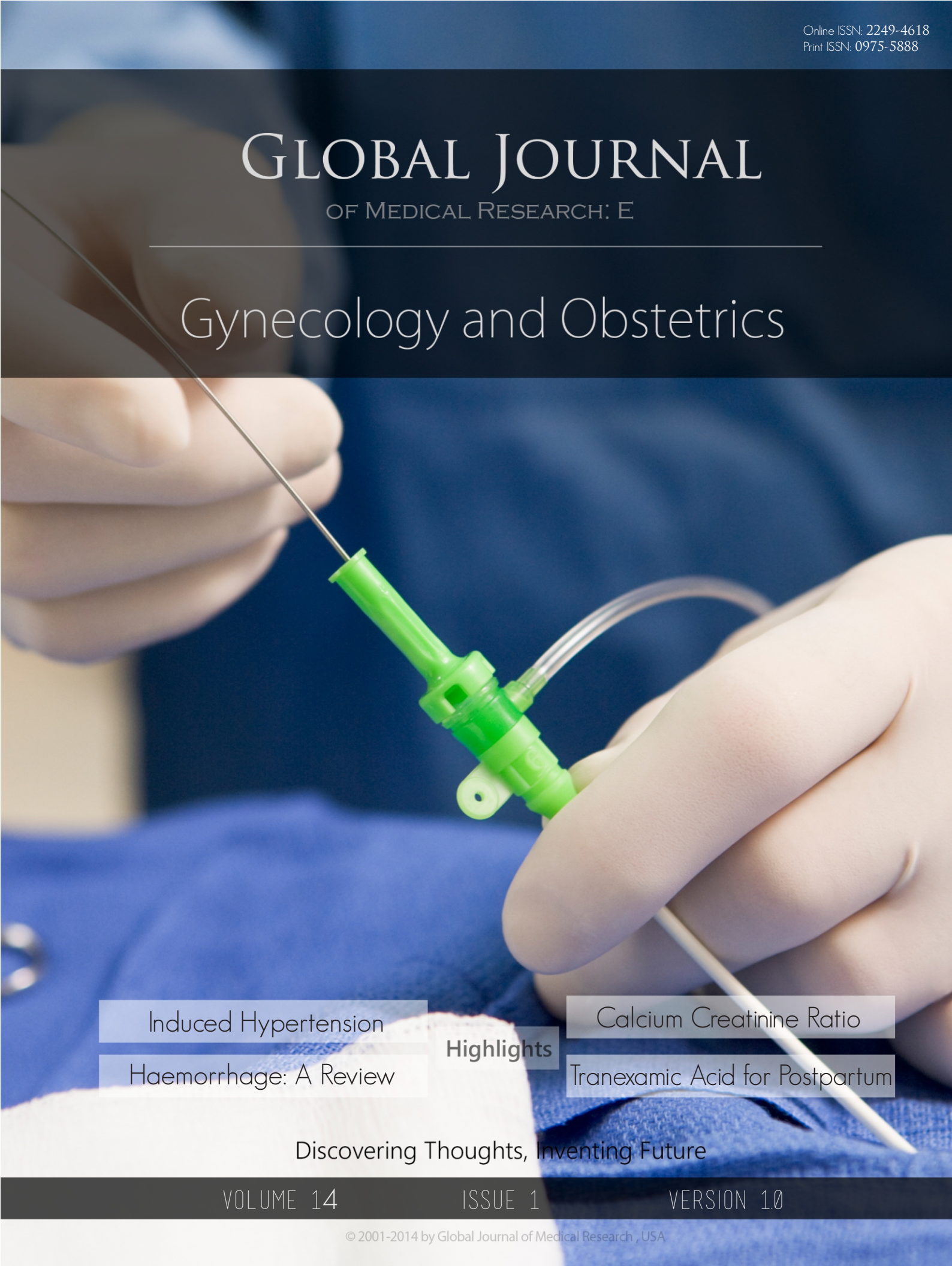

Induced Hypertension

Haemorrhage: A Review

Highlights

Calcium Creatinine Ratio

Tranexamic Acid for Postpartum

Discovering Thoughts, Inventing Future

VOLUME 14 ISSUE 1 VERSION 1.0

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Gynecology and Obstetrics

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# Evaluation of Oxidative Stress and Urinary Calcium Creatinine Ratio in Pregnancy Induced Hypertension

By Dr. Babli Yadav, Dr. Sangita Paneri & Dr. Sumitra Yadav

*Govt. MGM Medical College, Indore, India*

*Abstract-* The present study has been undertaken to evaluate oxidative stress and urinary calcium creatinine ratio in pregnancy induced hypertension. Study was carried out in M.Y. hospital and M.G.M. medical college during 2012 to 2013. Study comprised 250 subjects 125 normal pregnant women without any complications were taken as control and 125 pregnant women with PIH were taken study cases. Normal Gynaecological examination & history based informations were taken from each subject. Fasting blood sample and morning urine samples were collected from each subject and blood samples were analyzed for free radical estimations and urine sample analyzed for calcium and creatinine.

Our study shows a significant change in free radical level and siginificant fall in urine calcium creatinine ratio as compared to control study concluded that PIH can be result of increased oxidative stress. In this condition change in urinary calcium creatinine ratio indicate its relation to renal system. Study conclude that by improving oxidative stress with proper antioxidant diet or therapy we can decrease or minimize the risk associated with PIH.

*Keywords:* *pre-eclampsia, urinary calcium, urinary creatinine, pregnancy induced hypertension.*

*GJMR-E Classification :* *NLMC Code: WJ 190, WQ 200*


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# Evaluation of Oxidative Stress and Urinary Calcium Creatinine Ratio in Pregnancy Induced Hypertension

Dr. Babli Yadav [α], Dr. Sangita Paneri [σ] & Dr. Sumitra Yadav [ρ]

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*Keywords: pre-eclampsia, urinary calcium, urinary creatinine, pregnancy induced hypertension.*

## I. Introduction

Pregnancy induced hypertension (PIH) still continues to be one of the most common complication of pregnancy [1,2,3],. Despite of so much research and changes in management it is still a leading cause of maternal morbidity and mortality [4,5,6]. Though the exact cause of PIH is unknown. A number of modalities of treatment are being tried to decrease the progress of PIH [7,8,9]. In pregnancy induced hypertension endothelial cell dysfunction is a key event and this endothelial cell dysfunction may be associated with oxidative stress and addition to that calcium and creatinine ratio is as important aspect of maternal and fetal physiology during gestation so in order to evaluate oxidative stress and urinary calcium creatinine ratio in pregnancy induced hypertension was planned.

## II. Material and Methods

The study was conducted on total 250 patients who have been admitted in the Department of Obstetrics and Gynecology MGM Medical College and associate MY hospital Indore from July 2012 to may 2013. 125 normal pregnant women were taken as control and 125 pregnancy induced hypertensive women taken as study cases. A detailed history about age, residence, literacy, occupation etc. was noted with general physical and obstetric examination. Blood samples and spot urine were collected from each subject. Blood samples were analyzed for free radicals levels by Thiobarbituric acid reactive substance estimation urine samples were analyzed for calcium and creatinine levels by fully automated biochemistry analyzer.

*Table 1 :* Comparison of urinary calcium to creatinine ratio between normotensive pregnant women and PIH patients

| Parameters | Control n=125 | PIH cases n=125 | p value |
|---|---|---|---|
| Urinary calcium/creatinine ratio | 0.0618±0.0084 | 0.0370±0.0064 | <0.001 |

*Table 2 :* Comparison of free radicals level between Normotensive pregnant women and PIH women

| Parameter | Control n=125 | PIH cases n=125 | p value |
|---|---|---|---|
| Plasma MDA Nmol/ml | 2.8±0.48 | 5.2±0.92 | <0.001 |

## III. Results

The result of this study presented in the table-1 and table-2. The significant decrease in urinary calcium and creatinine ratio was observed in PIH women when compared to control and the significant increase level of MDA level was observed in PIH women when compared to control.

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## IV. Discussion

Pregnancy induced hypertension is a multifaceted syndrome with involvement of several important organs [10,11]. PIH is also associated with endothelial dysfunction [12,13,14]. Our study revealed that there was significant increase in MDA levels was observed there is reasonable evidence to suggest that circulating neutrophils of patient with preeclampsia release an excess of reactive oxygen species [15,16,17], present study revealed decrease calcium creatinine ratio observed in PIH women. Different studies concluded that calcium homoeostasis is an important aspect of maternal and fetal physiology during gestation [18,19,20,21]. A certain calcium level is required for production of endothelial derived releasing factor which maintains vasodilation in normal pregnancy. Alteration of calcium metabolism has been implicated in pathogenesis of hypertension during pregnancy. Study concluded that the pregnancy induced hypertension is associated with increased oxidative stress and disturb calcium creatinine ratio so addition antioxidant in treatment of PIH we can minimize the risk associated with PIH.

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# Intoxication with Magnesium Sulfate in the Treatment of Eclampsia a Propos of Three Cases and Review of the Literature

By S. Mezane, M. Achnani, M. Ziyadi, A. Babahabib, R. Hafidi, D. Moussaoui & M. Dehayni

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*Abstract-* Hypertensive diseases of pregnancy are among the first causes of severe maternal morbidity and mortality especially in developing countries. In developed countries, eclampsia is a rare event, but remains responsible for a significant maternal mortality. For over a century, magnesium sulfate is widely used in the United States in many obstetric indications including the treatment of eclampsia crises. There appears to be no consensus to treat or prevent seizures by magnesium sulfate. However, a large, multicentre, randomized trial compared the efficacy of magnesium sulfate with diazepam or phenytoin in eclamptic women. In this trial, magnesium sulfate was associated with a significantly lower rate of recurrent seizures and lower rate of maternal death than that observed with other anticonvulsants. The main objective of magnesium sulfate prophylaxis in women with preeclampsia is to prevent or reduce the rate of eclampsia and complications associated with eclampsia.

*Keywords: magnesium sulfate; preeclampsia; eclampsia, intoxication, treatment.*

*GJMR-E Classification : NLMC Code: WJ 140*

# Intoxication with Magnesium Sulfate in the Treatment of Eclampsia a Propos of Three Cases and Review of the Literature

## Intoxication au Sulfate de Magnésium dans le Traitement de L'éclampsie a Propos de 3 cas Et Revue de la Littérature

S. Mezane [α], M. Achnani [σ], M. Ziyadi [ρ], A. Babahabib [ω] , R. Hafidi [¥] , D. Moussaoui [§] & M. Dehayni [χ]

*Resume-* Les pathologies hypertensives de la grossesse figurent parmi les premières causes maternelles de morbidité sévère et de mortalité particulièrement dans les pays en voie de développement. Dans les pays développés, l'éclampsie est un événement rare, mais demeure responsable d'une mortalité maternelle non négligeable.

Depuis plus d'un siècle, le sulfate de magnésium est largement utilisé aux États-Unis dans de nombreuses indications obstétricales dont le traitement des crises d'éclampsie. Il ne semble pas exister de consensus pour traiter ou prévenir les convulsions par le sulfate de magnésium. Cependant, un essai randomisé, multicentrique, de grande taille a montré que les patientes traitées par sulfate de magnésium ont présenté une réduction significative du risque de récurrence des convulsions par rapport aux patientes traitées par diazépam ou phénytoïne.

De plus, le sulfate de magnésium a été associé à une diminution non significative de la mortalité maternelle. L'objectif principal de la prophylaxie par le sulfate de magnésium parmi les femmes pré éclamptiques est d'éviter ou de réduire le taux d'éclampsie et de complications associées à l'éclampsie. Cependant, plusieurs arguments viennent pondérer une large utilisation de cette molécule : la très faible prévalence de l'éclampsie dans les pays industrialisés, l'absence d'effet du sulfate de magnésium sur la mortalité et la morbidité périnatales, des effets secondaires nombreux, parfois graves comme la dépression respiratoire. La prescription de sulfate de magnésium doit donc dépendre du rapport bénéfices/risques qui est directement corrélé à la prévalence de l'éclampsie selon le groupe de risque considéré. Malgré plusieurs méta-analyses et études randomisées méthodologiquement inattaquables ayant démontré ses bénéfices dans le traitement et la prévention de l'éclampsie, et malgré les Recommandations pour la Pratique Clinique de plusieurs sociétés savantes ayant formalisé ses modalités d'utilisation, l'emploi de cette molécule reste controversée.

Beaucoup d'obstétriciens considèrent que les risques inhérents à cette thérapeutique demeurent supérieurs à ses bénéfices. Cela amène à s'interroger sur la place de ce traitement dans la prévention de la survenue d'une première crise d'éclampsie. Nous rapportons trois observations de l'intoxication par sulfate de magnésium dans le traitement de la pré-éclampsie.

*Mots clés: sulfate de magnésium; pré-éclampsie; eclampsie, intoxication, traitement.*

*Abstract-* Hypertensive diseases of pregnancy are among the first causes of severe maternal morbidity and mortality especially in developing countries. In developed countries, eclampsia is a rare event, but remains responsible for a significant maternal mortality. For over a century, magnesium sulfate is widely used in the United States in many obstetric indications including the treatment of eclampsia crises. There appears to be no consensus to treat or prevent seizures by magnesium sulfate. However, a large, multicentre, randomised trial compared the efficacy of magnesium sulfate with diazepam or phenytoin in eclamptic women. In this trial, magnesium sulfate was associated with a significantly lower rate of recurrent seizures and lower rate of maternal death than that observed with other anticonvulsants. The main objective of magnesium sulfate prophylaxis in women with preeclampsia is to prevent or reduce the rate of eclampsia and complications associated with eclampsia.However, several arguments balance a wide use of magnesium sulfate: the prevalence of eclampsia in the Western world is very low, the use of magnesium sulfate does not affect the neonatal morbidity and mortality, and it is associated with a high rate of side effects, sometimes severe, such as respiratory depression. Prescription the magnesium sulfate must depend the benefit / risk is directly correlated to theprevalence of eclampsia in the risk group considered report. Despiteseveral meta-analyzes and randomized studies methodologically unassailable with proven benefits in the treatment and prevention of eclampsia, despite the Guidelines for Clinical Practice of several learnedsocieties have formalized its Terms of Use, the use of this molecule remains controversial.

Many obstetricians consider that the risks of this treatment outweigh the benefits. This raises questions on the role of this treatment in preventing the occurrence of eclampsia. We report three cases of poisoning by magnesium sulfate in the treatment of pré-eclampsia.

*Keywords: magnesium sulfate; preeclampsia; eclampsia, intoxication, treatment.*

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## I. Introduction

L'éclampsie est une complication grave de la pré-éclampsie responsable d'une mortalité maternelle et infantile élevée. Ellereste encore fréquente dans les pays en voie de développement. L'amélioration du pronostic passe par la prévention avec un suivi précoce et régulier des gestantes. Elle nécessite un traitement adapté de l'hypertension gravidique ainsi que la prise en charge précoce de la pré-éclampsie et de l'éclampsie, avant l'installation des signes de gravité.

Le magnésium, sous la forme de sulfate de magnésium (MgSO4), a longtemps été utilisé par les anesthésistes-réanimateurs et les obstétriciens, de façon empirique, au cours de la crise d'éclampsie.

Ces dernières années, de nombreux travaux ont montré l'importance du magnésium dans le domaine de la cardiologie. C'est un antagoniste physiologique du calcium et un agent anti arythmique majeur, notamment pour les torsades de pointes.

En réanimation, les déficits en magnésium sont relativement fréquents, mais demeurent trop souvent méconnus ; l'hypomagnésémie pourrait être associée à une augmentation de la morbidité et de la mortalité des patients de réanimation. La difficulté majeure reste l'estimation correcte du capital magnésien du patient dueaux nombreuses intoxications observées. Nous rapportons trois cas de ces intoxications ;

## II. Observations

*a) Premièreobservation*

Madame R.B …âgée de 31ans,4èmegeste 3ème pare, consulte à 25 SA pour des signes neurosensoriels faites de céphalées, bourdonnements d'oreilles et brouillards visuels associées à des épigastralgies,vomissements et Œdèmes des Membres Inférieurs (OMI) d'évolution progressive depuis une semaine. L'examen à l'admission retrouve une patiente consciente, bien orientée dans le temps et l'espace, eupneique à l'air ambiant, Tension Artérielle TA=15/10 avec OMI et albuminurie =+++ au labstix.

Sur le plan obstétrical, la hauteur utérine correspond à l'âge gestationnel, Bruits Cardiaques Fœtaux (BCF) positifs, absence de contractions utérines, col long fermé postérieur, poche des eaux intactes. L'échographie obstétricale a montré une grossesse mono fœtaleévolutive, placenta antero-fundique, liquide amniotique en quantité normale, biométrie correspondant à l'âge gestationnel.

La patiente à été mise sous ALDOMET 500mg 3f/jour. Plus tard, elle a présenté toutefois une crise convulsive pour laquelle a été mise sous : MgSO4 dose de charge 4g dans 250cc SG5%, puis dose d'entretien, soit 1g/h à la seringue auto-pulséSAP pendant 48h.

Le bilan biologique montre une cytolyse hépatique GOT/GPT=183 /106, le reste du bilan reste sans anomalies.

*L'évolution est marquée par:*

- un déficit moteur et une hypertonie des quatre membres.
- des Réflexes Ostéotendineux (ROT) et la sensibilité sont normaux et pas de troubles de conscience.
- la TDM cérébrale a objectivé une ischémie cérébrale diffuse.

La décision était d'arrêter le sulfate et la mise en place de son antidote, le calcium. L'évolution a été favorable sur le plan maternel : une bonne récupération avec rééducation aubout de 7 jours. Mais sur le plan fœtale : mort fœtale in utero MFIU, la patiente est sortie 10jours après son admission.

*b) Deuxième observation*

Madame F.A …âgée de 29ans, primipare, sans antécédents pathologiques notables, admise pour éclampsie sur une grossesse de 29SA (une seule crise). L'examen à l'admission retrouve une patiente consciente, bien orientée dans le temps et l'espace, eupneique à l'air ambiant, TA=20/10, Saturation Artérielle en O2 SPO2=98%, Fréquence Cardiaque FC =101b/min avec OMI et albuminurie =+++ au labstix en plus des signes neurosensoriels positifs.

Sur le plan obstétrical : la hauteur utérine correspond à l'âge gestationnel, BCFpositifs, pas de contractions utérines, col long fermé post, poche des eaux intactes, à l'échographie obstétricale : grossesse monofoetale évolutive, placenta anterofundique, liquide amitotique en quantité normale, biométrie correspondant à l'âge gestationnel.

Le bilan biologique à été sans particularité.La patiente àété mise sous : MgSO4 dose de charge 4g dans 250cc SG5% puis dose d'entretien soit 1g/h à la Seringue Auto-Pulsé (SAP) pendant 48h.

*L'évolution est marquée par :*

- un déficit moteur et hypertonie des quatre membres.
- les ROT et la sensibilité sont normaux et pas de troubles de conscience.
- Au plan respiratoire, la patiente a présenté une détresse respiratoire avec un Œdème aigue pulmonaire (OAP).

La décision était d'arrêter le sulfate et la mise en place de son antidote : le calcium. L'évolution a été favorable sur le plan maternel : une bonne récupération avec rééducation au bout de 7jours, mais sur le plan fœtale : MFIU, la patiente est sortie 10jours après son admission.

*c) Troisième observation*

Madame K.A …âgée de 26ans, primipare, sans antécédents pathologiques notables, admise pour éclampsie sur une grossesse de 36SA (3 crises). L'examen à l'admission retrouve une patiente inconsciente (RASS=-1), désorientée dans le temps et l'espace, eupneique à l'air ambiant, TA=15/10,

SPO2=98%, FC=101b/min avec OMI et albuminurie =+++ au labstix en plus des signes neurosensoriels positifs. Sur le plan obstétrical : la hauteur utérine correspond à l'âge gestationnel, BCF positifs, pas de contractions utérines, col long fermé postérieur, poche des eaux intactes, à l'échographie obstétricale : grossesse monofoetale évolutive, placenta anterofundique, liquide amniotique en quantité normale, biométrie correspondant à l'âge gestationnel.

La patiente à été mise sous : MgSO4 dose de charge 4g dans 250cc SG5%, puis dose d'entretien soit 1g/h à la SAP pendant 48h. Le bilan biologique montre une cytolyse hépatique GOT/GPT=64 /102, le reste du bilan reste sans anomalies.

*Après 8h du sulfate, l'évolution est marquée par :*

- un déficit moteur et hypertonie des quatre membres.
- une abolition des ROT.

La décision était d'arrêter le sulfate et la mise en place de son antidote : le calcium. La patiente a bénéficié d'une césarienne en urgence donnant naissance à un nouveau-né bien portant. L'évolution a été favorable sur le plan maternel : une bonne récupération avec rééducation au bout de 7jours, la patiente est sortie 10jours après son admission.

## III. Discussion

*a) Le sulfate magnésium en obstétrique*

Les sels de magnésium restent très largement utilisés en obstétrique dans l'hypertension artérielle, de la pré-éclampsie et de l'éclampsie. Ce traitement a été propose par voie intrathécale depuis 1906, puis par voie veineuse à partir de 1925[1].

Il s'agit d'une molécule largement répandue dans les pays anglo-saxons. Sa place initialement revendiquée dans la tocolyse[2] est, en fait, très contestée dans cette indication car il n'a pas vraiment fait la preuve de sa supériorité [3]. Son indication reste essentiellement la pré- éclampsie sévère en prévention de l'éclampsie et surtout en prévention de la récidive de la crise d'éclampsie [4,5].

Les sels de magnésium sont des agents tocolytiques et vasodilatateurs [1]. Ils diminuent la pression artérielle sans modifier le débit sanguin utérin [6]. Ils ont par ailleurs un effet préventif et curatif sur le spasme vasculaire cérébral responsable des convulsions observées dans ces états [7]. Leur action inhibitrice sur l'hémostase et la coagulation présente un intérêtsupplémentaire. Sans être à proprement parler des anticonvulsivants, ils gardent toute leur place dans ce contexte. Les doses utilisées sont souvent très importantes : 6 gde MgSO4 suivie d'une perfusion de 2g/h. Ils nécessitent une surveillance clinique, électro cardiographique et biologique stricte.

Leur caractère protecteur neurologique [8,9] semble alors dans cette indication particulièrement intéressant jusqu'à avoir été préconisé comme anticonvulsivant idéal [10]. Sans aller jusqu'au sulfate de magnésium systématique qui n'a probablement pas d'intérêt majeur dans les pré-éclampsies modérées [11], cette molécule réduit significativement le risque de récurrences d'éclampsie (RR = 0,41 ; 95 % IC :0,32—0,51) ainsi que la mortalité maternelle (RR = 0,62 ;95 % IC : 0,39—0,99) par rapport aux autres anticonvulsivants[12].

Aussi, il faut noter que le sulfate de magnésium a des effets secondaires, le plus souvent mineurs, essentiellementà type de nausées et flushs. Certains effets secondaires majeurs comme la détresse respiratoire et l'hémorragie de la délivrance sont cependant très rares. [13,14]. En effet, une toxicité grave est possible, même si elle exceptionnelle, moyennant une surveillance adaptée des patientes. Néanmoins, des accidents rares sévères avec morts maternelles par surdosage ont été rapportés [15] justifiant des recommandations rigoureuses dans la surveillance.

Le sulfate de magnésium est donc un traitement qui doit rester dans la panoplie thérapeutique obstétricale, probablement sous-utilisée en France, mais qui doit être réservée aux formes sévères [16] et précoces de pré-éclampsiepour gagner le temps de la corticothérapie.

Une revue de synthèse sur le sulfate de magnésium permet de faire le point sur cette molécule. Le schéma de prescription recommandé aujourd'hui ne retrouve pas de consensus quant au moment optimal pour débuter le sulfate de magnésium, la dose de charge et d'entretien, la voie d'administration (IM ou IV) ou la durée de traitement[17].

Cependant dans les essais ayant utilisé la voie I.V, la dose d'attaque a varié de 4 à 6 g sur 20 à 30 minutes. Et la dose d'entretien a varié d'une à deux heures. Il y a eu significativement plus d'effets secondaires avec la voie intra musculaire : 28 % versus 5 %.

En cas de césarienne, la perfusion était débutée au moins une heure avant l'intervention et poursuivie pendant la césarienne [17].

Des bénéficesnéonatals sont égalementdémontrés: amélioration du score d'Apgar, réduction de l'incidence d'hospitalisation en unitéde réanimationnéonatale.

*b) Les effets indésirables du Sulfate de Magnésium*

Les effets indésirables sont pour la plupart liés aux propriétés de la molécule sur les cellules neuro-excitables. Ils sont pour la majorité d'entre eux sans conséquence sur le pronostic maternel. Duley et al (2003) ont colligé six essais contrôlés (11 444 patientes). Ceux-ci ont comparé le sulfate de magnésium au placebo ou à l'absence de traitement dans la prévention de l'éclampsie en cas de pré éclampsie [18].

Cette méta-analyse retrouvait globalement beaucoup plus d'effets secondaires chez les femmes traitées par sulfate de magnésium que chez celles ayant reçu le placebo ou n'ayant aucune thérapeutique (24% versus 5 %, avec une prévalence d'un effet indésirable pour six traitements.

Ces résultats doivent toutefois être pondérés puisqu'aux doses thérapeutiques utilisées, il s'agit principalement de bouffées de chaleur et de flushs cutanés. Les autres troubles sont beaucoup moins fréquents : nausées et vomissements, hypotension artérielles, hypotonies musculaires avec troubles de l'élocution et somnolence et irritations au site d'injection en cas d'administration musculaire.

En cas de surdosage, il se produit généralement une disparition des réflexes ostéotendineux (étonnamment aussi fréquente dans le groupe placebo) et rarement une dépression respiratoire [18]. Ces surdosages sont le plus souvent la conséquence d'erreurs dans les posologies ou les vitesses de perfusion [19]. Ces complications sont habituellement régressives dès l'arrêt de la perfusion sans utilisation du gluconate de calcium, antidote spécifique du sulfate de magnésium, exceptionnellement utilisé (0,3 %) [18]. Une surveillance clinique rapprochée des réflexes ostéotendineux, de la fréquence respiratoire et de la conscience est suffisante, mais indispensable [20]. La magnésémie n'a pas sa place dans la surveillance thérapeutique sauf peut-être dans de rares cas où la fonction rénale et la diurèse sont altérées.

L'existence indéniable d'effets secondaires impose de n'utiliser le sulfate de magnésium que dans le cadre d'un protocole thérapeutique bien établi avec un respect strict des modalités d'utilisation (posologie, surveillance) et surtout des indications pour lesquelles le rapport bénéfices-risques dutraitement est largement favorable. Ce rapport dépend directement du risque de survenue d'éclampsie selon la présence ou non de signes de gravité [21]. Ainsi, les femmes présentant des signes évocateurs d'une éclampsie imminente (hyperréflexie ostéotendineuse, céphalées, troubles visuels), et plus encore lorsqu'ils sont associés, sont les meilleures candidates pour bénéficier du sulfate de magnésium [20,22]. Dans ces cas et sous réserve d'une surveillance stricte, les risques d'effets secondaires graves seraient faibles. Les résultats d'une étuderétrospective sur 57 pré-éclampsies sévères traitées par sulfate de magnésium ont montré l'inexistence d'effetssecondairesgraves hormis un surdosage à l'origine d'une aréflexie régressive à l'arrêt de la perfusion sans recours au gluconate de calcium [23].

*c) Les modalités thérapeutiques et de surveillance du sulfate de magnésium*

Les modalités d'utilisation du sulfate de magnésium sont actuellement codifiées par des recommandations d'experts publiées en 2009 [20]. Pour la prévention de l'éclampsie, la plupart des auteurs associent une dose de charge de 4 g intraveineuse administrée en 15 à 30 minutes suivie d'une perfusion d'entretien de 1 à 2 g/h pendant au moins 24 heures [24, 20,10]. Les débits de perfusion doivent être contrôlés parune seringue autopulsée. La durée du traitement, qu'il ait été débuté avant ou après l'accouchement, ne fait pas l'objet d'un consensus. Dans la plupart des essais randomisés, le traitement est poursuivi pendant 24 heures [25, 24,26]. Deux études récentes ont suggéréla possibilité d'arrêter la perfusion dès la disparition des signes fonctionnels, le contrôle de la tension artérielle et l'apparition de la crise polyurique (diurèse de plus de 100 ml/h pendant au moins 2 heures) [27,28].

La surveillance de la patiente pendant toute la durée du traitement par sulfate de magnésium doit être continue, monitorée sous scope, et surveillance de la SpO2 compte tenu des risques de dépression respiratoire. Elle doit être complétée par la surveillance horaire des réflexes ostéotendineux, car le premier signe de surdosage est leur abolition (qui justifie l'arrêt de la perfusion). Le dosage de la magnésémie est indiqué en cas de signes cliniques de surdosage (troubles de conduction, arrêt respiratoire, abolition des réflexes ostéotendineux) ou d'une créatinémie supérieure à 150 µmol/l. L'antidote est le gluconate de calcium (deux ampoules) qui doit être disponible à tout moment.

## IV. Conclusion

L'utilisation du sulfate de magnésium en pratique courante est simple et les complications imputables au traitement semblent exceptionnelles sous réserve d'une utilisation rationnelle et parfaitement codifiée. Sous couvert d'indications restreintes aux formes sévères de pré éclampsie comportantdes signes d'irritabilité neurologique faisant craindre l'imminence d'une crise d'éclampsie (céphalées, troubles visuels, exagération des réflexes ostéotendineux), le bénéfice de ce traitement est démontré.

Dans un futur proche, il est probable que les détracteurs du sulfate de magnésium devront battre en retraite car d'autres bénéfices néonatals majeurs de ce traitement semblent avérés dans le domaine de la neuroprotection cérébrale. Prescrit en intraveineux juste avant un accouchement prématuré imminent, il réduirait nettement le risque de paralysie cérébrale chez les grands prématurés.

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# Flow Nipples and Breast Cancer: Value of Senologicalassessment About 40 Cases and Review of the Literature

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*Abstract-* Nipple discharge is defined as the outcome of a liquid by a variable aspect pore galactophoric outside of lactation and postpartum, c 'is a frequent reason for consultation en senology(3rd complaint breastafter mastodyniaand themasses),The pathologic nipple discharge is defined as a spontaneous flow, unilateral, usually unipore and not milky;although benign etiology in most cases, it may also be a telltale sign of breast cancer. Our retrospective study, involving 40 cases of pyramidectomy performed in 40 patients hospitalized and treated in the service of gynecology and obstetrics at the University Hospital HMIMV RABAT, over a period of 11 years from January 2000 to October 2012, aimed to compare radioclinical data and cytologic to histologic findings and the literature data.In this study it was noted the following characteristics: age, history, clinical, mammography ultrasonography, cytology, galactography, the surgical procedure, the final histology.

*Keywords: flow nipple, cancer, mammography, cytology, galacto-mri, histology.*

*GJMR-E Classification : NLMC Code: QZ 20.5, WP 840*

# Flow Nipples and Breast Cancer: Value of Senologicalassessment About 40 Cases and Review of the Literature

## Ecoulements mamelonnaires et cancer du sein : Valeur du bilan sénologique A propos de 40 cas et revue de la littérature

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*Abstract-* Nipple discharge is defined as the outcome of a liquid by a variable aspect pore galactophoric outside of lactation and postpartum, c 'is a frequent reason for consultation en senology(3rd complaint breastafter mastodyniaand themasses),The pathologic nipple discharge is defined as a spontaneous flow, unilateral, usually unipore and not milky;although benign etiology in most cases, it may also be a telltale sign of breast cancer.

Our retrospective study, involving 40 cases of pyramidectomy performed in 40 patients hospitalized and treated in the service of gynecology and obstetrics at the University Hospital HMIMV RABAT, over a period of 11 years from January 2000 to October 2012, aimed to compare radio-clinical data and cytologic to histologic findings and the literature data.In this study it was noted the following characteristics: age, history, clinical, mammography ultrasonography, cytology, galactography, the surgical procedure, the final histology.

Nipple discharge was more likely to be related to breast cancer, as in our study, there was a telltale sign of cancer in 4 cases, it is necessary to achieve a balance of complementary imaging to identify and locate the lesion at the origin of the flow.Imperfect sensitivity and specificity of these tests and the technical constraints of galactography have recently led to the search for new exploration flow nipple namely methods: galactoscopy; breast MRI.

*Keywords: flow nipple, cancer, mammography, cytology, galacto-mri, histology.*

*Resume-* L'écoulement mamelonnaire se définit comme étant l'issue d'un liquide d'aspect variable par un pore galactophorique en dehors de la lactation et du post-partum ;c' est un motif de consultation fréquent en sénologie (3éme plainte mammaire après les mastodynies et les masses), L'écoulement mamelonnaire pathologique se définit par un écoulement spontané, unilatéral, habituellement unipore et non lactescent ; bien que d'étiologie bénigne dans la majorité des cas, il peut également être un signe révélateur de cancer du sein Notre travail rétrospectif, portant sur 40 cas de pyramidectomie pratiquée chez 40 patientes hospitalisées et traitées au service de la gynéco-obstétrique à l'Hôpital Militaire d' Instruction Mohamed V CHU RABAT, sur une période de 12ans allant du janvier 2000 à octobre 2012 , avait pour but de comparer les données radio-cliniques et cytologique aux résultats histologiques ainsi qu'aux données de la littérature.Au cours de cette étude on a été précisé les caractéristiques suivantes : âge, antécédents, la clinique ; les résultats de la mammographie, de l'échographie, de la cytologie, de la galactographie, du geste opératoire et enfin les résultats de l'histologie définitive.

Un écoulement mamelonnaire a d'autant plus de risque d'être en rapport avec un cancer du sein, comme dans notre étude, il était un signe révélateur de cancer dans 4 cas, Il est donc nécessaire de réaliser un bilan d'imagerie complémentaire afin d'identifier et de localiser la lésion à l'origine de l'écoulement.Les faibles sensibilités et spécificités de ces différents examens ainsi que les contraintes techniques de la galactographie, ont conduit récemment à la recherche de nouvelles méthodes d'exploration des écoulements mamelonnaires à savoir : la galactoscopie ; l'IRM mammaire.

*Most Cles: ecoulement mamelonnaire, cancer, mammographie, cytologie, galacto-irm, histologie.*

## I. Introduction

L'écoulement mamelonnaire est un motif de consultation fréquent en sénologie (3éme plainte mammaire après les mastodynies et les masses), L'écoulement mamelonnaire pathologique se définit par un écoulement spontané, unilatéral, habituellement unipore et non lactescent ; bien que d'étiologie bénigne dans la majorité des cas, il peut également être un signe révélateur de cancer du sein.

Il est donc nécessaire de réaliser un bilan d'imagerie complémentaire afin d'identifier et de localiser la lésion à l'origine de l'écoulement. La prise e charge radiologique habituelle d'un écoulement mamelonnaire comprend un bilan sénologique classique avec mammographie +/- échographie suivi d'une galactographie.

Les faibles sensibilités et spécificité de ces différents examens ainsi que les contraintes techniques de la galactographie ont conduit récemment à la recherche de nouvelles méthodes d'exploration des écoulements mamelonnaires ; plusieurs techniques font l'objet de publications, parmi celles-ci on trouve :

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-l'échographie (galactographie écho guidée, cytoaspiration écho guidée, macro biopsies sous échographie….) ;
-la galactoscopie ;
-l'IRM mammaire seule ou couplée à des séquences de galacto-IRM.

## II. Materiels et Methodes

Notre travail porte sur l'étude rétrospective de 40 cas de pyramidectomie pratiquée chez 40 patientes hospitalisées et traitées au service de la gynéco-obstétrique à l'HMIMV CHU RABAT, sur une période de 12ans allant du janvier 2000 à octobre 2012.

*Pour les critères d'inclusion :*

- Ecoulement séro-hématique ou sanglant.
- Avec ou sans masse palpable.
- Bénéficier toutes d'une pyramidectomie.

Au cours de cette étude on a été précisé les caractéristiques suivantes :

- L'âge
- Les antécédents
- La clinique
- La mammographie et l'échographie
- La cytologie
- La galactographie
- Le geste opératoire
- L'histologie définitive
- L'évolution

## III. Resultats

*a) Aspects épidémiologiques*

1. La fréquence : dans notre série, l'écoulement sanglant ou séro-hématique représente 80% de motif de consultation.
2. L'âge : l'âge moyen de nos patientes est de 47,5ans avec des extrêmes de 25ans et 62ans.
3. La Parité : 77 ,5% sont des multipares (plus de 3 enfants) ; et 7 ,5% sont des nulligestes.
4. L'Allaitement : 29sur 40 de nos patientes avaient allaite leurs enfants.
5. Le Statut hormonal : 45% de nos patientes sont ménopausées soit 18 patientes, 14 patientes sont sous contraception et le reste soit 3 patientes sont suivi pour infertilité primaire.
6. Les Antécédents : 2 patientes ayant la notion du cancer du sein chez une cousine de 1er degré.

Pour les résultats de la clinique et les examens complémentaires sont les suivantes :

*b) La clinique*

- ✓ le caractère de l'écoulement il est unipore chez 32 patientes, multi pore chez 4 patientes, spontané chez 8 patientes, provoqué chez 29 patientes et séro-sanglant chez toutes les patientes.
- ✓ les adénopathies, absentes chez toutes nos patientes.
- ✓ les nodules palpables, pas de nodule chez toutes nos patientes.

*c) La mammographie*

Pratiquée chez toutes nos patientes, elle a été normale chez 22 de nos patientes soit 55% et pathologique chez 15 patientes, elle a montré les anomalies suivantes :

- Dilatation galactophorique chez 4 patientes
- Calcifications chez 7 cas
- Opacités : 3 cas
- Dystrophie fibrokystique : 1 seul cas

*d) La galactographie: Pratiquée que dans 31cas et elle a montré :*

- 13 cas d'ectasie canalaire
- 11 cas de papillome intra-canalaire
- 4 cas de sténose
- Normale dans 8 cas
- Non concluante dans le reste

*e) L'échographie*

Pratiquée chez 19 patientes, elle a montré des canaux galactophoriques dilatés chez 8 cas et normale dans le reste.

*f) La cytologie*

Réalisée chez 29 cas : Normale dans 09 cas et Interprétable (lame acellulaire) dans 10 cas.
Dans les autres cas l'examen avait montré :

- 2 cas de cellules galactophoriques suspectes
- 4 cas sans anomalies cyto-nucléaires ; en faveur de papillome
- 5 cas de cellules spumeuses

*g) Le traitement*

Toutes nos patientes sont bénéficiées d'une pyramidectomie : la pièce est envoyée pour étude histologique.

*h) L'histologie définitive*

Elle a montré 4 cas de pathologie épithéliale maligne dont 3 cas de carcinome intra-canalaire multifocale avec foyer infiltrant, et 1 cas de carcinome intra-canalaire in situ. Pour la pathologie épithéliale bénigne tumorale, elle a montré 9 cas de papillome et pour la non tumorale, elle a montré 11 cas d'ectasie canalaire, 7 cas de dystrophie fibrokystique et 3 cas d'hyperplasie épithéliale.

## IV. Discussions

L'écoulement mamelonnaire est un motif de consultation fréquent en sénologie (3éme plainte mammaire après les mastodynies et les masses) il représente 3 à 15% de la symptomatologie mammaire [1], l'écoulement pathologique se définit par un écoulement spontané, unilatéral, habituellement unipore et non lactescent.

Le caractère sanglant de l'écoulement semble être péjoratif pour la plupart des auteurs, c'est ainsi que SALMON [2] a proposé la technique de l'hémocult permettant la mise en évidence du sang dans l'écoulement en consultation.

Dans notre série, le caractère séro-sanglant de l'écoulement a été présent chez toutes nos patientes, le pic de fréquence des écoulements dans notre série est de 47,5ans en accordavec plusieurs auteurs dont la moyenne d'âge se situe aux alentours de 45ans avec des extrêmes de 15 et 83ans ; [3 ,4 ,5]

Mais, les études récentes montrent qu'il ne doit pas tenir compte de l'âge dans l'interprétation d'un écoulement mamelonnaire.

Bien que d'étiologie bénigne dans la majorité des cas, il peut également être un signe révélateur de cancer du sein, et ceci qu'il que soit le caractère de l'écoulement (tableau1).

*Tableau 1 :* Caractère de l'écoulement

| Caractère de L'écoulement | BERMOND [3] cancer | NOTRE SERIE cancer | BERMOND [3] Lésions bénignes | NOTRE SERIE Lésions bénignes |
|---|---|---|---|---|
| Sanglant | 17 | 3 | 24 | 40 |
| Non sanglant | 4 | - | 26 | - |
| Spontané | 29 | 3 | 65 | 8 |
| Provoqué | 1 | - | 8 | 29 |
| Unilatéral | 19 | 3 | 65 | 32 |
| Bilatéral | 2 | - | 9 | 4 |
| Unicanalaire | 20 | 3 | 61 | 32 |
| Pluricanalaire | 1 | - | 13 | - |

Il est donc nécessaire de réaliser un bilan d'imagerie complémentaire afin d'identifier et de localiser la lésion à l'origine de l'écoulement, la prise en charge radiologique habituelle d'un écoulement mamelonnaire comprend un bilan sénologique classique avec mammographie +/- échographie suivi d'une galactographie.

*a) La mammographie*

C'est l'examen complémentaire de base en sénologie, il semble indispensable de réaliser des mammographies devant tout écoulement malgré le pourcentage élevé de mammographie normale pour plusieurs raisons :

- ✓ intérêt de diagnostic préopératoire en montrant des micro calcifications.
- ✓ intérêt de dépistage : l'écoulement peut survenir sur des seins à risque et il est permet de visualiser le parenchyme adjacent et controlatéral à l'écoulement.

Dans notre série, la mammographie était normale dans 22 cas, mais dans les 3cas de cancer elle a montré des micro calcifications suspectes dans 2 cas ; et dans l'autre cas des calcifications rondes de type bénin.

*b) L'échographie*

C'est un examen peu cité par les auteurs dans le cadre des écoulements mamelonnaires, elle peut mettre en évidence : ectasie canalaire, kystes, nodules échogénes (VPP 70% contre 50% à la galactographie) [12]

*c) La galactographie*

Actuellement c'est l'examen de référence pour la recherche et la caractérisation de lésions à l'origine d'un écoulement mamelonnaire, elle a pour but l'opacification de l'arbre galactographique, afin d'en montrer la forme, le contenu et l'harmonie [6,7], elle comporte toutefois certains inconvénients :

- ✓ c'est une technique invasive qui nécessite l'insertion d'un petit cathéter au niveau d'un poremamelonnaire et l'injection de produit de contraste intra-galactophorique. Elle expose donc aux risques d'échec de cathétérisme et d'extravasation de produit de contraste.
- ✓ Elle nécessite que l'écoulement soit présent le jour de l'examen
- ✓ Elle ne permet pas de différencier lésions bénignes et malignes.
- ✓ Possède des contre-indications à savoir : allergie à l'iode, état inflammatoire, écoulement purulent [8]
- ✓ A éviter dans les lésions malignes cliniquement et mammographiquement évidentes. Ainsi, elle est inutile dans les galactorrhées. [9 ,7]

Dans notre étude, la galactographie n'a été pratiquée que dans 36 cas et elle a montré les anomalies suivantes : 13 cas d'ectasies canalaires, 11 cas de papillome intra-canalaire, 4 cas de sténose, normale dans 8 cas.

*d) La cytologie*

L'examen cytologique s'applique, soit aux écoulements mamelonnaires, soit au matériel rapporté par cytoponction à l'aiguille fine. [12]

L'analyse cytologique doit être pratiquée dés que l'écoulement est constaté en consultation. Elle devient de plus en plus fiable au fur et à mesure que les cliniciens affinent leur technique de prélèvement et que le laboratoire en analyse un grand nombre [10].

Dans notre étude, la cytologie n'a été pratiquée que dans 29cas, et elle a montré : 2 cas des cellules galactophoriques suspectes, 4 cas en faveur de

papillome, 5 cas de cellules spumeuses, interprétables (lames acellulaires) dans 9cas, normale dans 9cas.

Mais dans la littérature, la plupart des auteurs confirment que la cytologie n'a qu'une valeur relative, avec de faux positifs et de faux négatifs et ces résultats ne changent ni l'indication ni la technique opératoire ,par contre pour d'autres, elle garde un certain poids comme une méthode d'exploration complémentaire indispensableà l'étude de tout écoulement mamelonnaire isolé lorsque les examens cliniques, mammographiques et cytologiques ne «parlent »pas.

En réalisant un moule interne de l'arbre galactophorique, elle fournit des renseignements sur la composante épithéliale que la mammographie peut passer sous silence, c'est l'intérêt de sa complémentarité.

*e) Nouvelles techniques d'explorations*

i. *La galactoscopie avec biopsie intra-ducale* l'objectif de cette technique est de diminuer le nombre d'indications chirurgicales.

L'étude qui a été réalisée par HUNERBEIN (2006) (38 patientes avec écoulement mamelonnaire), montre les résultats suivants:

- galactoscopie positive pour 29 patientes (78%),
- biopsies réussies dans tous les cas sauf 1,
- 2 prélèvements non représentatifs.

Pour les résultats histologiques / biopsies : 22 papillomes ; 2 carcinomes in situ ; 2 carcinomes invasifs, tous ces résultats sont confirmés par l'histologie de la pièce dans tous les cas. HUNERBEIN BREAST CANC RES TREAT 2006

La galactoscopie est une technique en développement néanmoins les données sont insuffisantes, elle peut aider au bilan préopératoire des lésions intracanalaires, aucune étude n'a montré sa supériorité par rapport à la galactographie.

L'IRM :sensible avec une bonne valeur prédictive négative, mais les faux négatifs concernent les carcinomes de bas grade ou les petits carcinomes infiltrants

L'IRM est trop peu spécifique car elle est moins performante que la galactographie pour le diagnostic différentiel, mais elle serait intéressante couplée à la galactographie pour évaluer l'étendue des lésions.

La galacto-IRM : utilise une séquence à forte pondération T2 (séquence galactographique) qui permet une étude non invasive des canaux galactophores dilatés qui sont visibles sous forme de structures tubulées en hyper signal. [12]

Comme pour la galactographie, les lésions intragalactophoriques apparaissent sous forme d'un défect de signal, d'une irrégularité de paroi ou d'une obstruction canalaire (arrêt brusque).

La proportion non négligeable de cancer du sein parmi les patientes présentant un écoulement mamelonnaire (-10%) justifie la réalisation d'explorations complémentaires visant à détecter et à caractériser les lésions responsable de ce symptôme, la galacto-IRM semble pouvoir répondre à ces attentes. [12]

L'intérêt de l'examen réside dans le couplage de la séquence galactographique avec des séquences « classique » d'IRM mammaire- dont l'injection dynamique de Gadolinium-permettant la caractérisation de la lésion responsable de l'écoulement mamelonnaire (critères de bénignité /malignité, extension…)

*Cette technique présente plusieurs avantages*

- elle permet une cartographie des anomalies galactophoriques de manière non invasive,
- elle fournit des éléments de caractérisation des intra-ducales responsables de l'écoulement (critères morphologiques et de cinétique de rehaussement).
- elle apporte au clinicien une vision claire et facilement exploitable de l'ensemble des anomalies, grâce à la fusion des séquences galactographiques et des séquences injectées.
- elle offre une alternative à la galactographie aux patientes pour lesquelles celle-ci n'est pas réalisable (mamelon ombiliqué, écoulement intermittent, échec de cathétérisme…) prélèvements non représentatifs. [12]

*f) Traitement Chirurgical*

Dans le cas des écoulements mamelonnaires sans tumeur papable, l'intervention de choix pratiquée par la plupart des auteurs est la pyramidectomie classique réalisée sous anesthésie générale ou locale [6,7] Il a un double but diagnostique et thérapeutique. Si un territoire se révèle suspect (micro calcifications, opacité repérée à la mammographie, tumeur palpable), il conviendra de pratiquer une tumorectomie ou une quadrectomie partielle, dirigée par un repérage préalable, avec examen extemporané [4] ;Pour ce dernier, il est nécessaire seulement s'il existe une masse palpable cliniquement ou repérer en per-opératoire [4] ceci pour la plupart des auteurs, dans les autres cas, au contraire il ne faut pas demander un examen extemporané parce que les lésions sont minimes, fragiles, difficiles à trouver et demandant de nombreuses coupes qui massacrent la pièce ainsi les minimes tumeurs intra-galactophoriques sont perdues pour un examen ultérieur [11].

Pour le résultat esthétique, il est d'autant acceptable que le volume du sien est important, que l'exérèse est limitée et qu'il n'y a pas de complication hémorragique ou infectieuse. A distance, la cicatrice est quasiment invisible pour un examinateur non averti [7,6].

L'allaitement maternel dans des grossesses ultérieures n'est pas contre-indiqué et restera possible si l'opérateur a préservé les autres canaux lactifères.

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## V. Conclusion

La proportion non négligeable de cancer du sein parmi les patientes présentant un écoulement mamelonna ire (10%) justifie la réalisation d'explorations complémentaires visant à détecter et à caractériser les lésions responsables de ce symptôme [12],bien qu'au terme du bilan étiologique, le clinicien est orienté vers la pathologie en cause, la hantise de méconnaitre un cancer du sein l'amène presque toujours à la chirurgie qui permet d'avoir un diagnostic de certitude ,mais actuellement les nouvelles techniques d'exploration à savoir la galactoscopie et la galacto-IRM permet de poser le diagnostic avant l'acte opératoire .

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# "Assessment of Fetal Brain Vascularization using Three-Dimensional Power Doppler Ultrasound Angiography in Pregnancies Affected by Late-Onset Fetal Growth Restriction"

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*Summary-* 28 fetuses affected by late onset (34-36 weeks of gestation) growth restriction and 77 appropriate for gestational age fetuses (AGA) have been enrolled .

*Objectives:* Aim of this study is to explore the possible use of 3D power Doppler ultrasound angiography (3D-PDA) in the assessment of cerebral blood flow distribution in growth restricted fetuses (FGR) compared to normal fetuses.

*Methods:* 28 fetuses affected by late-onset FGR (34-36 weeks) and 77 appropriate for gestational age fetuses (AGA) were enrolled. Two regions of interest (ROI) of the fetal brain were scanned. The first ROI (named Frontal Zone), sprinkled mainly by anterior cerebral artery (ACA) and the second ROI, (named Temporal Zone), sprinkled by middle cerebral artery (MCA). We analysed 3D-Power Doppler Angiography (PDA) indexes: VI (vascularization index), FI (flow index), VFI (vascularization-flow index).

*GJMR-E Classification : NLMC Code: QZ 20.5, WP 840*


*Strictly as per the compliance and regulations of:*

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Alberto Rossi [α], Irene Romanello [σ], Leonardo Forzano [ρ], Martina Cecchia [ω], Guido Ambrosini [¥] & Diego Marchesoni [§]

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*Results:* All the fetuses included in the late-onset FGR group had normal UA PI and normal MCA PI. Instead, VI and VFI values were increased in the Frontal Zone and decreased in the Temporal Zone comparing with the control group.

*Conclusions:* 3D-PDA of fetal brain could recognize regional variations of brain perfusion in late-onset FGR without any pathological 2D Doppler. The phenomenon of preferential increment in blood supply to the frontal region ("frontal brain sparing effect") may protect general cognitive functions, occurring while MCA PI has not demonstrated signs of deterioration yet.

## I. Introduction

Three dimensional ultrasound examination has been introduced to evaluate fetal blood flow and vascularization in several organs, such as kidneys, liver and brain [1] in normal pregnancies. Moreover this technique has been applied to assess placental circulation.

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An estimated fetal weight (EFW) less than the 10th percentile has been most widely applied as the threshold to define FGR, according to ACOG guidelines. [2]

Fetal growth restriction is characterized by important haemodinamic changes, with a redistribution of blood flow towards vital organs, such as brain, heart and adrenals despite other districts (abdomen). This blood flow centralization process is defined as "brain sparing effect", traditionally identified by a reduced Doppler pulsatility (PI) in the middle cerebral artery (MCA).

FGR affects 5-10% of pregnancies and represents mainly a complication of placental dysfunction. It is associated with significant perinatal mortality and morbidity and even increased risk for poor long-term outcomes, involving general cognitive competence.

Overt brain lesions such as hypoxic-ischemic encephalopathy, intraventricular hemorrhage and leukomalacia can occur in up to 15% of all FGR fetuses, while a substantial proportion of FGR infants could present subtler neurobehavioral disturbances.3,4

Chronic hypoxia due to placental insufficiency cause a blood flow centralization process, also known as "brain-sparing effect", which has been considered an adaptative response of the fetus, in order to maximize brain oxygen supply. It has been classically identified by reduced Doppler pulsatility index (PI) in the middle cerebral artery (MCA).5-8

Two different populations of fetal growth restricted fetuses have been identified depending upon the gestational age in which FGR occurs. These populations present different patterns of deterioration that can be investigated in multiple vascular beds, using power Doppler ultrasound. Early-onset FGR, presenting before 34 gestational weeks, is first characterized by an escalation in blood flow resistance in umbilical artery (UA), accompanied by vasodilatation of MCA, then followed by deterioration of venous Doppler parameters

and biophysical profile score (BPS). In late-onset FGR, beyond 34 gestational weeks, normal or only mildly elevated UA Doppler parameters with an isolated MCA vasodilatation can be found.9

The main purpose of antenatal surveillance remains the identification of the best moment for delivery balancing neonatal and fetal morbidity and mortality.

The aim of this study is to explore the possible use of 3D power Doppler ultrasound angiography (3D-PDA) using VOCAL software (GE Healthcare, USA) in the assessment of different cerebral regions in late-onset growth restricted fetuses versus normal ones.

## II. Materials and Methods

Between January 2011 and February 2012 a group of 28 consecutive cases of singleton pregnancies affected by late onset (34-36 weeks of gestation) growth restriction and 77 appropriate for gestational age fetuses (AGA) have been enrolled in the study.

FGR is defined as an ultrasound-estimated fetal weight below the 10th percentile for gestational age according to the Hadlock 4 equation, using biparietal diameter (BPD), head circumference (HC), abdominal circumference (AC) and femur length (FL).10

We enrolled only fetuses with a late-onset growth restriction, that is to say it has occurred after 34 gestational weeks9, and with a maximum gestational age of 36 weeks.

Exclusion criteria were as follows: 1) multiple pregnancy, 2) fetal malformation or chromosomal defects, 3) maternal complications, 4) conception by assisted reproductive techniques.

All ultrasound examinations were performed by a single operator (A.R.) using General Electric E8 (General Electric Corp. Milkwaukee, WI, USA) with a 5MHz trans-abdominal probe equipped with automatic volume measurements, colour, pulsed and power Doppler options.

Before starting the 3D examinations we calculated fetal biometry ( BPD, HC, AC, FL, EFW), amniotic flow volume and maternal uterine arteries Doppler.

Pulsed-wave Doppler flow analysis of the umbilical artery (UA) was obtained from a free-floating central section of the cord with an angle close to 0°, while the middle cerebral artery (MCA) was sampled at the proximal end of the vessel close to the circle of Willis with an insonation angle of about 0°. Three subsequent blood velocity waveforms for each vessel were analyzed for PI according to Gosling et al.11

We checked the results against previously published reference ranges12-13 and defined abnormal Doppler when PI showed at least 20% deviation from the mean value.14

The introduction of 3D power Doppler (3D-PD) and the vascularization histogram allowed to quantify the vascularization and blood flow to the placenta and several fetal organs.

Moreover, power Doppler does not show aliasing effect and the colour map is independent of insonation angle.15

The use of 3D-PD is particularly useful in the evaluation of fetal brain vessels because of their small caliber. 3D-PDA images of the fetal brain were acquired during fetal rest, using the same presets for each acquisition. The angle of acquisition was set at 35°, the pulsed repetition frequency (PRF) of the power Doppler at 0.9. We chose the biparietal plane including landmarks like the thalami, the third ventricle, the cavum septi pellucidi (CSP), the tentorial hiatus and a symmetrical display of the calvaria for recording power Doppler signals.

After displaying three simultaneous perpendicular planes on the monitor (axial, sagittal and coronal) the size of the region of interest (ROI) was adapted manually to created the two zones of the fetal brain to be analyzed (Fig. 1). These two ROI were defined by using anatomy landmarks to ensure a good reproducibility of this method among different operators. The first ROI is the Frontal Zone (zone 1), which has been obtained by tracing the contour of the anterior part of the fetal brain up to the perpendicular line crossing the anterior edge of the CSP (Fig.2). The second ROI, Temporal Zone (zone 2), is defined by a rectangle reaching from both temporal bones with the width of CSP included (Fig.3).

The volume of the investigated zones and the blood flow indexes were calculated using VOCALTM software. A rotation step for each contour plane was selected with a 30° angle chosen arbitrarily. This procedure of rotating the reference plane was done until a full rotation of 180° was achieved. The fetal brain volumes were calculated after all contour traced (6 steps). Eventually, the Vocal Histogram switch was activated for the automatic calculation of the 3D-PDA vascular indexes. Three vascular indexes were generated: vascularization index (VI) defined as the percentage of power Doppler data (coloured voxels) within the volume of interest; flow index (FI), the mean signal intensity (average colour value) of the power Doppler information; vascularization-flow index (VFI), a combination of both factors derived through their multiplication.16

Inter- and intraobserver reproducibility was assessed with the intraclass correlation coefficient.

Difference between AGA and growth-restricted fetuses were evaluated using Student's test. $P<0.05$ was considered significant.

The study was approved by the local Ethics Committee and written consent was obtained from all participants.

## III. Results

A total of 105 pregnant women with a gestational age ranges from 34+0 to 36+0 weeks were included in the present study. The mean maternal age was 30.6±3.1; 43% of the women was primigravida and 57% was multigravida respectively; a total of 46% was primipara whereas 54% was multipara.

All the fetuses included in the late-onset FGR group (28 fetuses) had normal UA PI and normal MCA PI.

In the table 1 are reported the values of the vascular parameters (VI, FI, VFI) in Frontal Zone (zone 1) for the FGR group and the control group. VI and VFI were both increased in the FGR group with statistical significance comparing to control group ($P<0.05$).

Table 2 shows the values of VI, FI, VFI in Temporal Zone (zone 2) for FGR group and control group. VI and VFI were significantly decreased in the FGR group comparing to the control group.

## IV. Discussion

In our study all the fetuses with late-onset FGR demonstrated no alterations in bidimensional Doppler. In late-onset FGR cardiovascular abnormalities are typically more subtle and do not extend beyond the cerebral circulation.9,17 Almost all clinical studies have focused on the assement of MCA Doppler, which is still considered as the clinical standard for the hemodynamic evaluation of the fetal brain.8 Indeed, the "brain-sparing" onset has been classically identified by a reduction in MCA PI.5-7

However, recent longitudinal studies based on power Doppler evaluation of different brain arteries in growth restricted fetuses emphasize that MCA PI is reduced in a later stage than the anterior cerebral artery (ACA). It probably means that brain blood perfusion in FGR follows an internal regional redistribution, which changes with the progression of hypoxic fetal deterioration.3,18-20

Our findings agree with these observations. The VI and VFI we obtained by 3D-PDA seem to demonstrate regional changes in blood perfusion, which appears increased in the Frontal Zone (zone 1) and decreased in the Temporal Zone (zone 2) respectively, compared with the control group. The VI has been suggested to be representative of the number of vessels in the ROI21, but recently Jones et al.16 specified that an increased VI in the ROI can be due both to an increased dimension of a vessel (vasodilatation) and to diversion to other vessels secondary to pressure rise, showing a strong linear relationship to volume flow rates.22 In contrast, FI is less predictable and seems to have a more complex, non-linear relationship to flow rates.17 VFI obviously feels the effects of both previous indexes.

The initial preferential increment in blood supply to the Frontal Zone can be associated with preservation of general cognitive functions such as impulse control, language, memory, problem solving and suggests a hierarchical order in the protection of brain functions.23 Moreover, three dimensional indices were easy to obtain and showed a high level of intra- and interobserver repeatability as reported in previous papers (24) .

With this in view, MCA vasodilatation (MCA PI reduction) may do not represent a protective response but rather the starting point after which the protection of the frontal area begins to decline. The real "brain-sparing effect" seems to be marked by hemodynamic changes in the anterior cerebral artery (ACA) and consequently in its districts. If confirmed, these findings might have important implications, especially since Doppler findings may be subtle and accurate identification of growth restriction arising in the third trimester still provides a challenge. The clinical significance of the observations reported in the present study remains to be established by larger prospective studies with long term postnatal neurological follow-up.

Finally, according to the results we obtained in this study, 3D sonography and power Doppler angiography can be considered as new techniques offering additional vascular parameters allowing for detection of early non invasive "brain sparing markers" in fetuses affected by FGR, even without any pathological 2D Doppler velocimetry. Construction of reference charts and interobserver variability study of 3D-PDA vascular indexes of fetal brain circulation in normal pregnancies need to be planned.

## V. Acknowledgments

The Authors report no conflicts of interest.

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*Table 1 :* VI, FI and VFI in Frontal Zone (Zone ) for the Control Group and for the late-onset (>34 wks) FGR group

| FRONTAL ZONE (ZONE 1) | VI | FI | VFI |
|---|---|---|---|
| Late-onset FGR (28 | **5,5* (2,1)** | 24,3 (5,9) | **1,4* (0,8)** |
| fetuses) | | | |
| Control Group (77 fetuses) | 2,3 (0,4) | 32,0 (7,5) | 0,7 (0,4) |

** P<0,05 vs Controls (Student's t-test) and p<0,05 vs Group 1(ANOVA)*

*Table 2 :* VI, FI, VFI in Temporal Zone for the Control group and for the late-onset FGR

| TEMPORAL ZONE (ZONE 2) | VI | FI | VFI |
|---|---|---|---|
| Late-onset FGR (28 fetuses) | 0,9* (0,3) | 29,5 (7,5) | 0,2* (0,1) |
| Control Group (77 fetuses) | 3,4 (0,7) | 27,7 (6,0) | 1,2 (0,4) |

** P<0,05 vs Controls (Student's t-test) and p<0,05 vs Group 1(ANOVA)*

FIGURES SECTION

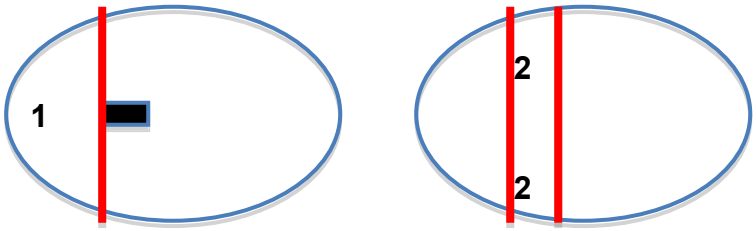


*Fig 1 :* CSP: cavum septi pellucidi. 1: "Frontal zone", 2: "Temporal zone"

= **CSP**

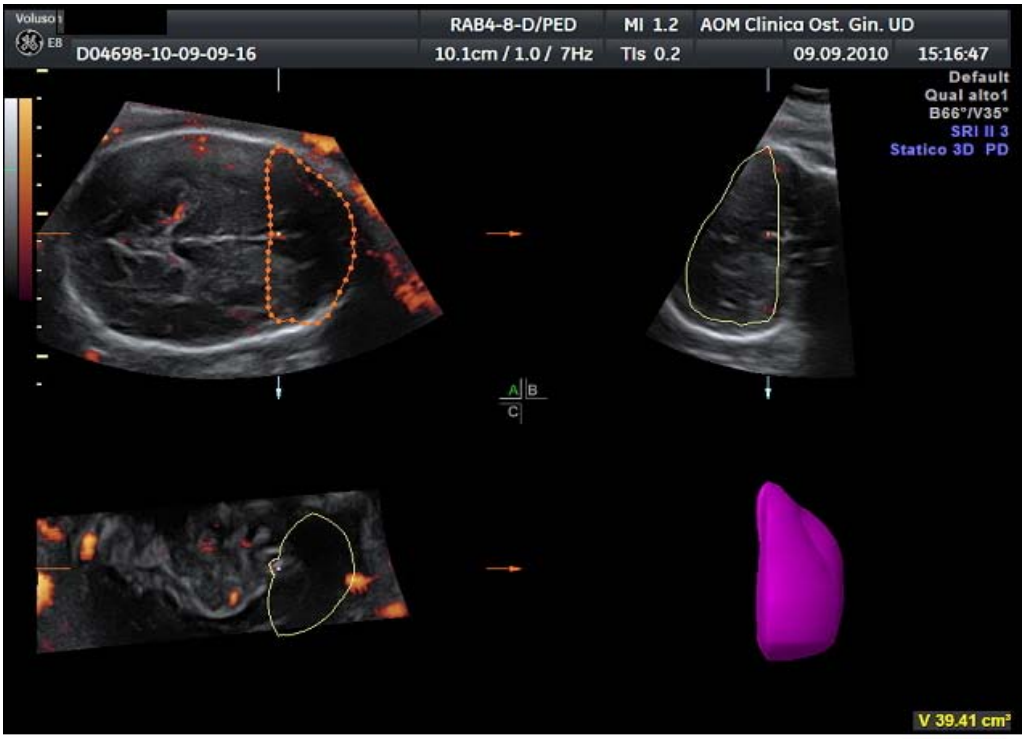


*Fig. 2 :* 3D-PDA of Zone 1 "Frontal Zone"

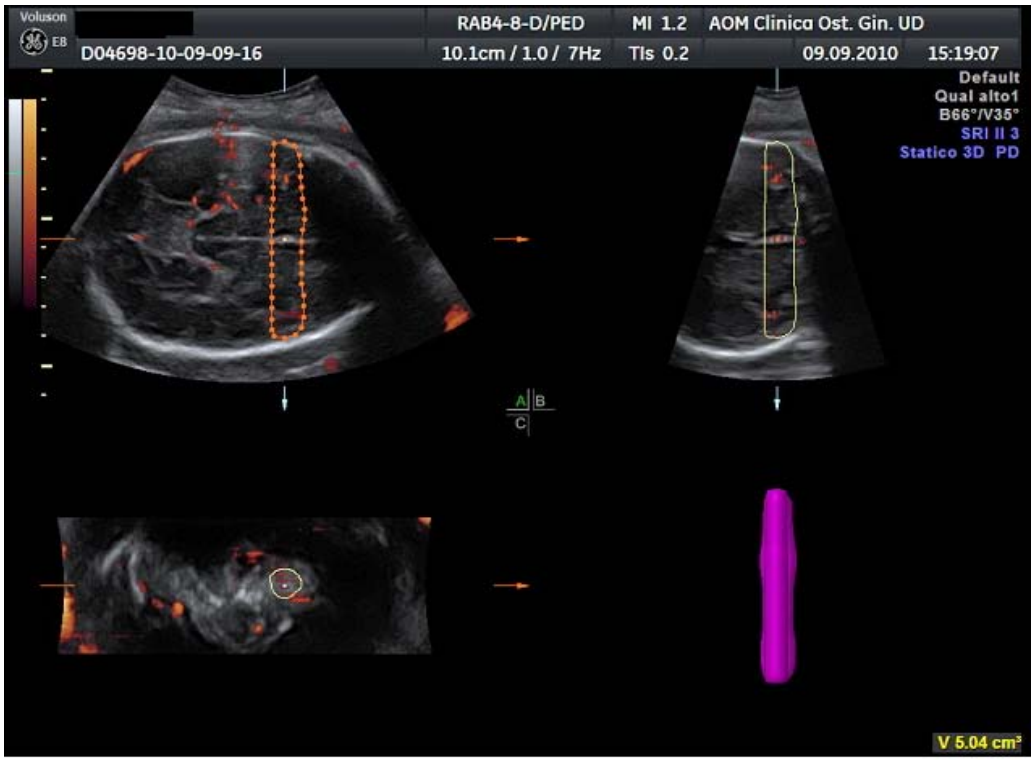


*Fig. 3 :* 3D-PDA of Zone 2 "Temporal Zone"

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# Study of Feto-Maternal Outcome in Pregnancy Induced Hypertension

By Dr. Maimoona Ahmed & Dr. Rekha G. Daver
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*Abstract-* *Introduction:* Pregnancy induced hypertension is one of the most common causes of both maternal and fetal morbidity and mortality. This study aims to determine the feto-maternal outcome and correlation with severity of PIH.

*Material and Methods:* 250 cases of PIH were studied and divided according to severity. The maternal and fetal outcome parameters were documented and analysed using statistical methods.

*Results:* More the severity of PIH, more are the chances of maternal and fetal complications. Earlier onset of PIH was also seen more in severe cases as were the number of inductions.

*Conclusion:* T he clinical course of PIH is progressive and is characterised by continuous deterioration that is ultimately stopped only by delivery. Early detection and appropriate management of the pregnancy may improve the outcome for both the mother and the fetus.

*Keywords:* *pregnancy induced hypertension, maternal outcome, fetal outcome.*

*GJMR-E Classification :* *NLMC Code: WP 650*


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## I. Introduction

Pregnancy induced hypertension is one of the most common causes of both maternal and fetal morbidity and mortality. It is a pregnancy – specific syndrome that can virtually affect every organ system. It is a challenge to be addressed and overcome if there is to be any significant improvement in maternal and perinatal health.

Although the cause of PIH still remains unknown, evidence for its manifestation begins early in pregnancy. Covert pathophysiological changes occur that gain momentum across gestation and eventually become clinically apparent. Unless delivery supervenes, these changes ultimately result in multi – organ involvement with a clinical spectrum ranging from barely noticeable to one of cataclysmic deterioration.

Eclampsia, disseminated intravascular coagulopathy, acute renal failure, HELLP syndrome, intra - cerebral haemorrhage, antepartum haemorrhage and even maternal death can occur. Long term complications like persistent hypertension and cardiovascular morbidity are known risks for the mothers suffering from PIH.

Fetal complications like intra - uterine growth retardation, sudden intra - uterine fetal death, still births, preterm and low birth weight babies, increased need for NICU care, increased neonatal morbidity and mortality are prevalent.

An attempt has been made in the present study to identify the factors affecting feto – maternal outcome in cases of pregnancy induced hypertension so as to be able to identify them at the earliest and offer a better outcome to both mother and baby.

## II. Materials and Methods

This was a prospective study carried out over a period of 1 year from 1st Jan 2009 till 31st Dec 2009 at Grant medical college and Sir J. J. Group of hospitals after clearance from ethical committee. 250 patients of pregnancy induced hypertension were studied. They were divided into mild, moderate and severe PIH. The cases with systolic blood pressure greater than 130 mmHg, diastolic blood pressure greater than 90 mmHg on two measurements taken 6 hours apart, in association with proteinuria more than 300 mg in 24 hours urine were included in the mild preeclampsia group. The cases were accepted as mild preeclampsia if the the diastolic blood pressure was less than 100 mmHg and as moderate preeclampsia if the diastolic blood pressure was 110 mmHg. Severe cases were defined if the following criteria were present: Systolic blood pressure ≥ 160 mm Hg, Diastolic blood pressure ≥ 110 mm Hg and Proteinuria 3+ or more.

A prestuctured proforma was filled and parameters of maternal and fetal outcome were tabulated. Statistical tests like the Chi square test and calculation of Spearman's rho were applied. A p value < 0.001 was accepted as significant.The results obtained were compared with other studies from textbooks and journals.

## III. Results

There were 151 (60%) cases of mild PIH, 52 (21%) cases of moderate PIH and 47 (19%) cases of severe PIH.

107 i.e. 43% cases were in 21-25 yr age group, 62 i.e. 25% in the 26-30yr age group, 49 i.e. 19% in <20 yr and 33 i.e. 13 % were above 30 yrs. In 47 cases of severe PIH, 12 (25.5%) of the patients were in the ≤ 20 yrs age group, 19 (40.5%) were ≥ 30 yrs of age, whereas 8 (17%) were in the ages between 21-25 yrs and 26-30 yrs respectively.

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149 (60%) of the patients were primigravidae, 55 (22%) were of second gravida, 27 (11%) were G3 and 19 (7%) were grand multigravidae. 32 i.e. 68% of the patients with severe PIH were primigravidae and 5 (10.7%) were grand multigravidae. 6 (12.8%) and 4 (8.5%) were of the second and third gravida respectively.

155 i.e. 62% of the patients had > 3 ANC visits, 72 i.e. 28% had between 1 and 3 visits while 23 i.e. 9.2% were unregistered.

There is a significant negative correlation between the number of ANC visits and PIH severity when analysed statistically (Spearman's rho= -0.311, $p<0.001$).

Out of 250 cases, 81.2% had BMI in the normal range, 4.8% were underweight and 14% patients were overweight. No correlation was seen between BMI & severity of PIH (Spearman's rho= -0.046, $p=0.468$).

When the position of placenta was studied, lateral placenta was seen in 44.6% cases of severe PIH whereas only 17.14% of mild and moderate cases had lateral placenta. Thus we can see that in cases of severe PIH, the incidence of lateral position of placenta was significantly higher (Chi- square = 16.874, $p<0.001$).

Table no 1 : shows the maternal complication in the different classes of PIH.

*Table No 1 :* Maternal Complications

| COMPLICATIONS | MILD PIH | MODERATE PIH | SEVERE PIH |
|---|---|---|---|
| CCU ADMISSION | *0* | *0* | *3* ***(6.4%)*** |
| IMMINENT ECCLAMPSIA | *0* | *5* **(9.6%)** | *13* ***(27.8%)*** |
| *ECLAMPSIA* | *0* | *3* ***(5.8%)*** | *11* ***(23.4%)*** |
| *ABRUPTIO PLACENTAE* | *1* ***(0.7%)*** | *3* ***(5.8%)*** | *1* ***(2.1%)*** |
| *CEREBROVASCULAR ACCIDENT* | *0* | *0* | *1* ***(2.1%)*** |
| *DIC* | *0* | *0* | *1* ***(2.1%)*** |
| *ACUTE RENAL FAILURE* | *0* | *0* | *1* ***(2.1%)*** |
| *MORTALITY* | *0* | *1* ***(1.9%)*** | *2* ***(4.3%)*** |
| *TOTAL* | *151* | *52* | *47* |

In severe cases of PIH, there were CCU admissions in 6.4% cases, imminent ecclampsia in 27.8% cases and abruptio placentae, DIC, acute renal failure in 2.1% cases. Maternal mortality was seen in 4.3% cases.There is a significant positive correlation between occurrence of maternal complications & severity of PIH (spearman's rho= 0.532, $p<0.001$) i.e. more the severity of PIH, more are the chances of complications.

175 i.e. 70 % cases delivered spontaneously and 75 i.e. 30% needed induction.

When correlated with severity of PIH, 42 (89.3%) of severe PIH cases required induction, 26 (50%) of cases of moderate and 7 (4.6%) cases of mild PIH needed induction.There is a significant positive correlation between induction of labour and severity of PIH (spearman's rho = 0.729, $p<0.001$) i.e. Severe PIH cases needed to be induced. Out of all the cases, 153 i.e. 61.2% cases were delivered vaginally and 97 i.e. 38.8% required LSCS, the most common indication being fetal distress.

Table no 2 shows the fetal outcome. There was a significant negative correlation of severity of PIH with birth weights (Spearman's rho = -0.323, $p<0.001$). Thus cases of severe PIH had babies with lower birth weights. In our study, total 69 babies needed NICU admissions i.e. 27.6%. The most common reason for admission was preterm with low birth weight (52%). There is a significant positive correlation between NICU admissions & severity of PIH (spearman's rho= 0.261, $p<0.001$) i.e. severe cases of PIH needed more NICU admissions.

*Table No 2 :* Fetal Outcome

| Severity Of Pih | Birth Weight < 2 Kg | Small For Geestation Age Babies | Nicu Admission |
|---|---|---|---|
| MILD PIH | 13 **(8.6%)** | 19 **(12.6%)** | 27 **(17.9%)** |
| MODERATE PIH | 23 **(44%)** | 34 **(65.5%)** | 22 **(42.3%)** |
| SEVERE PIH | 36 **(76.6%)** | 38 **(80.9%)** | 20 **(42.6%)** |

Total fetal wastage seen in this study was 37 i.e. 14.8% of all cases as shown in Table no 3.There is a significant positive correlation between occurrence of fetal wastage & the severity of PIH (spearman's rho= 0.482, p<0.001) i.e. more the severity of PIH, more are the chances of fetal wastage.

*Table No 3 :* Fetal Wastage

| Fetal Wastage | Mild Pih | Mod Pih | Sev Pih | Total |
|---|---|---|---|---|
| Abortion | 1 | 0 | 8 | 9 |
| Fsb | 1 | 4 | 7 | 12 |
| Msb | 0 | 2 | 5 | 7 |
| Nnd | 0 | 4 | 5 | 9 |
| Total Number | 2 | 10 | 25 | 37 |
| Percentage | 1.3% | 19.2% | 53% | |

The gestational age of onset of PIH was compared in the 3 groups. In 22 (8.8%) cases, the onset was at < 28 wks, in 33 (13.2%) between 28 -32 wks, in 82 (32.8%) between 32 -36 wks and in 113 (45.2%) the onset was beyond 36 wks gestation.

In cases of severe PIH, the onset < 28 wks was seen in 31.9% cases whereas in mild PIH it was in 1.3% cases. There was a significant negative correlation between gestational of onset of PIH and severity of PIH (spearman's rho= - 0.467, p<0.001), thus showing that severe PIH cases have an earlier onset. Table no 4 and 5 show the correlation of age of onset of PIH with maternal and fetal outcome.

*Table No 4 :* Gestational Age Of Onset Of Pih And Maternal Outcome

| Age Of Onset | Maternal Complications | Induction Of Labour | Preterm Delivery | Lscs | Total Number |
|---|---|---|---|---|---|
| < 28 wks | 9 *(40%)* | 18 *(81.8%)* | 20 *(90.9%)* | 5 *(22.7%)* | 22 |
| 28 – 32 wks | 11 *(33.3%)* | 20 *(60.6%)* | 29 *(87.9%)* | 13 *(39.4%)* | 33 |
| 32 – 36 wks | 18 *(21.9%)* | 22 *(26.8%)* | 44 *(53.7%)* | 33 *(40.2%)* | 82 |
| >36wks | 7 *(6.2%)* | 15 *(13.3%)* | 0 | 46 *(40.7%)* | 113 |
| TOTAL | 45 | 75 | 93 | 97 | 250 |

*Table No 5 :* Gestational Age Of Onset Of Pih And Fetal Outcome

| Age Of Onset | Sga | Nicu Admission | Fetal Wastage | Total |
|---|---|---|---|---|
| < 28 wks | 14 *(63.6%)* | 8 *(36.4%)* | 16 *(72.7%)* | 22 |
| 28 – 32 wks | 19 *(57.6%)* | 18 *(54.5%)* | 7 *(21.2%)* | 33 |
| 32 – 36 wks | 32 *(39%)* | 20 *(24.4%)* | 8 *(9.8%)* | 82 |
| >36wks | 26 *(23%)* | 23 *(20%)* | 6 *(5.3%)* | 113 |
| TOTAL | 91 | 69 | 37 | 250 |

## IV. Discussion

Pregnancy induced hypertension is a pregnancy- specific multi system disorder affecting both the mother and the baby.

In our study, total 250 cases were classified as per severity of PIH. 151 (60%) patients had mild PIH. The rest were almost equally distributed as moderate or severe cases – 52 cases (21%) with moderate PIH and 47 cases (19%) with severe PIH. 20 patients i.e. 43% cases with severe PIH were in the extremes of age groups.

Eskenazi B, Fenster L et al in a multivariate analysis of risk factors of PIH in 1991 found that women that either spectrum of age were more susceptible to PIH. [1]

Similar findings were also seen in a study by C. J. Lee et al in a study for risk factors of PIH in the Asian population in 2000.[2]

PIH often affects young and nulliparous women and this was shown in our study as well as other studies done by Eskenazi B, Fenster L and Sidney S [1] and Campbell DM et al [3].

Antenatal care is one of the most important determinants of early detection of PIH. Regular visits will help identify such cases at the earliest and enable prompt intervention, thus improving the pregnancy outcome. In the present study, of all 250 cases,155 i.e. 62% had more than 3 ANC visits, 72 i.e. 28% cases had between 1-3 visits, while 23 i.e. 9.2% were unregistered that is they had not received any antenatal care. There was a significant negative correlation found in this study between number of ANC visits and PIH severity indicating that patients with fewer ANC visits had more severe PIH. Bandar Abbas et al in their study showed that women of PIH with IUGR babies had less than three antenatal visits during pregnancy. [4]

There was no correlation found between BMI and severity of PIH in this study. However other studies like Lisa et al [5] and Dorothea Mostello et al [6] have shown the increased incidence of PIH with higher BMI. Ahmet Ursavas reported obesity as an independent risk factor for PIH and preeclampsia in 2008. [7]

In our study, in cases of severe PIH the incidence of lateral placenta was significantly higher. This result is in accordance with the study of Kofinas et al [8] who state that of their preeclamptic women, 74% had unilateral placental location and a 2.8 fold risk of preeclampsia.

In our study, the total maternal complications seen were 45 i.e. in 18 % of the cases. 3 (1.2%) patients were admitted in the critical care unit, 18 (7.2%) had imminent eclampsia, 14 (5.6%) suffered from eclampsia, 4 (1.6%) had abruption placentae and disseminated intravascular coagulopathy and acute renal failure was seen in 1 (0.4%) case. In cases of severe PIH in particular, there were CCU admissions in 6.4% cases, imminent eclampsia in 27.8% cases and abruptio placentae, DIC, acute renal failure in 2.1% cases and mortality was seen in 4.3% cases.

Maternal mortality was seen in 3 (1.2%) cases. One such was of a second gravida with full term pregnancy with severe PIH and Intrauterine Fetal Demise. Patient had only 2 ANC visits. She had been brought to the hospital in DIC and was immediately admitted in the CCU. However despite blood product transfusion she went into Acute Renal Failure and could not be resuscitated. The second case was of a primigravida with 32 weeks pregnancy who presented with eclamptic convulsions and fresh still birth. In the third case, the patient had presented with severe PIH with term pregnancy with eclampsia. Emergency LSCS had been done which was uneventful. Patient was in the ward as the baby was in the NICU for preterm status. On day 18 post delivery, there was a sudden rise in her blood pressure which had previously come to normal post delivery. She suffered from a Cerebrovasclar accident and died despite immediate CCU transfer and resuscitation.

In the present study, there was a significant positive correlation between occurrence of maternal complications & severity of PIH (spearman's rho= 0.532, $p<0.001$) i.e. more the severity of PIH, more are the chances of complications. These were similar to results obtained by Yucesoy et al [9] and Yadav et al [10]. In cases of PIH, due to uteroplacental insufficiency, there are increased chances of intra – uterine growth restriction. Also in severe cases needing early induction, preterm births are common. Thus the babies are of lower birth weights.

In the present study, 113 i.e. 45.2% babies had birth weight > 2.5 kg, 65 (26%) between 2 – 2.5 kg, 29 (11.6%) between 1.5 – 2 kg, 28 (11.2%) between 1 – 1.5 g and 15 (6%) with < 1 kg. There was a significant negative correlation of severity of PIH with birth weights (Spearman's rho = -0.323, $p<0.001$). Thus cases of severe PIH had babies with lower birth weights. Ye RW et al [11] in their study in 2010 showed the incidence rates of low birth weights in mild, moderate, and severe subgroups as 2.5% 4.9% and 11.9% respectively. The rates increased with the severity of PIH. in another study by Buchbinder et al, they have shown that in women who have gestational hypertension or preeclampsia, increased rates of preterm delivery and delivery of small-for-gestational-age infants are present only in those with severe disorder. [12]

In our study, a significant positive correlation was seen between the NICU admissions and severity of the cases, i.e. severe PIH cases had more chances of the baby getting admitted in NICU which has also been studied by Ray et al [13].

Sudden vasospasm, chronic utero-placental and feto-placental insufficiency and complications like abruption placentae put the babies of PIH mothers at higher risk of perinatal mortality. In the present study, the fetal wastage like abortion, still births and neonatal deaths were studied and were seen more in severe cases of PIH. In studies by Yadav et al [10] and Yucesoy et al [9], perinatal mortality rate was found to be higher in severe cases of PIH.

In the present study, cases with earlier onset of PIH had a more severe course of the disease and increased maternal and fetal morbidity as also shown by study conducted by Ingrid PM et al [14].

Termination of pregnancy is the only cure for PIH. In milder cases if the fetus is premature, conservative management can be employed to reduce the risk of neonatal death or serious morbidity due to prematurity. In such cases assessment of fetal well being and placental function are done along with strict toxaemia monitoring of the mother. If the PIH does not improve or it worsens then the pregnancy has to be terminated irrespective of the gestational age to avoid

maternal complications and morbidity. In our study, in 144 i.e. 95.4% cases of mild PIH the patients were admitted and spontaneous labour was awaited and 7 i.e. 4.65 needed to be induced. In severe cases however, 42 i.e. 89.3% cases needed to be induced. There was a significant positive correlation between induction of labour and severity of PIH (spearman's rho = 0.729, $p<0.001$) i.e. severe cases of PIH had to be terminated resulting in preterm and low- birth weight babies. Similar results were seen in a study conducted by Bailey et al [15] and Ye RW et al [11] where cases of severe PIH had to be induced at an earlier gestational age as compared to the mild cases.

## V. Conclusion

The clinical course of PIH is progressive and is characterised by continuous deterioration that is ultimately stopped only by delivery. Emphasis should be on early registration and regular ANC visits so as to detect cases of pregnancy induced hypertension as early as possible in turn preventing severity and its associated complications. The fetal well being should be monitored with non stress tests, modified biophysical profile, serial USG with amniotic fluid estimation, Doppler studies so as to detect fetal compromise. Maternal parameters of blood pressure, proteinuria, serum uric acid levels as well as premonitory signs and symptoms should be monitored so as to decide a timely intervention for best feto – maternal outcome.

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# Tranexamic Acid for Postpartum Haemorrhage: A Review

By Suzanne Davis
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*Abstract-* Post partum haemorrhage is the main cause of maternal mortality worldwide. Tranexamic acid is a cheap, easy to use and relatively safe medication that is gaining popularity as a management option for obstetric haemorrhage. It is already widely used to limit bleeding in trauma and many major surgeries. This review examines the evidence surrounding its use to control bleeding at the time of delivery.

*Keywords: tranexamic acid, pregnancy, cesarean section, postpartum haemorrhage, bleeding, maternal mortality.*

*GJMR-E Classification : NLMC Code: WS 360, WJ 190*

*Strictly as per the compliance and regulations of:*

# Tranexamic Acid for Postpartum Haemorrhage: A Review

Suzanne Davis

*Abstract-* Post partum haemorrhage is the main cause of maternal mortality worldwide. Tranexamic acid is a cheap, easy to use and relatively safe medication that is gaining popularity as a management option for obstetric haemorrhage. It is already widely used to limit bleeding in trauma and many major surgeries. This review examines the evidence surrounding its use to control bleeding at the time of delivery.

*Keywords: tranexamic acid, pregnancy, cesarean section, postpartum haemorrhage, bleeding, maternal mortality.*

## I. Background

The 5thMillennium Development Goal is improving maternal health and more specifically decreasing by three quarters, the maternal mortality ratio by 2015. While important gains have been made, developing countries are still lagging due to the poor access to healthcare facilities, skilled healthcare workers, medications and blood products1.

The World Health Organisation defines post partum haemorrhage as a blood loss of greater than or equal to 500ml at the time ofor after delivery. Post partum haemorrhage remains the leading cause of maternal mortality and morbidity worldwide. The maternal mortality ratio worldwide is estimated at 210 maternal deaths per 100 000 live births, but is as high as 1100 in some developing, particularly African countries. This is in comparison to 7 maternal deaths per 100 000 live births in Australia and 21 in the United States2. Up to one third of these deaths may be attributed to obstetric haemorrhage, many of which may be prevented or minimized with timely access to medications and emergency care. Up to 1 percent of women having a vaginal birth and 5 percent of women having a cesarean section will require a blood transfusion, which exposes the woman to risks from transfusion reactions and transmission of blood-borne viral infections3. In many areas, blood products are simply not available.

The predominant causes of post partum haemorrhage are uterine atony, trauma to the genital tract and retained placental tissue after delivery. There are a number of factors that increase a woman's chance of having a post partum haemorrhage, however the majority of cases occur in women with low risk pregnancies.

Tranexamic acid is an antifibrinolytic that prevents the breakdown of fibrin deposits at bleeding sites in the body. By blocking lysine-binding sites on plasminogen molecules, the body's natural pro-hemostatic state post delivery is enhanced.

Tranexamic acid is already widely used in non-obstetric fields, to decrease bleeding from trauma and during elective cardiac and orthopedic surgery4,5. It has proven effectiveness in decreasing blood loss in patients with menorrhagia6. As there is very limited data from randomized controlled trials on the use of tranexamic acid for treating post partum haemorrhage, early reports of its success in preventing post partum haemorrhage, as well as evidence of its effective use in other areas of medicine allow extrapolation of the results to cases in which a post partum haemorrhage is already occurring. Tranexamic acid is cheap, easy to transport, store and use and evidence to date suggests that it is safe to use, even in pregnant women who are already at higher risk for thromboembolic events.

This report examines the existing data on the use of tranexamic acid in post partum haemorrhage, with an aim to recommend its use in limited settings as an adjunct to established interventions such as uterotonics.

## II. Evidence

The most recent Cochrane review on the literature surrounding the effectiveness of tranexamic acid in either preventing or treating post partum haemorrhage was undertaken in 20113. Since then seven further small but promising trials have given further strength to the evidence that the medication is effective in obstetric bleeding related to delivery. As not enough evidence is available to identify an impact on maternal mortality, the outcomes specifically ascertained in this review are reduction in blood loss, avoidance of further interventions and decreased requirement for blood transfusion. Data on adverse reactions and associated events was also collected.

Nine of the elevenrandomized controlled trials identified for inclusion in this review were studies in which tranexamic acid was given prophylactically prior to lower segment cesarean section. Despite the fact that most gave inadequate or unclear data on randomization or blinding techniques (or were not blinded), the limited

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available data on the subject necessitates consideration of all trials in the review.

Of the two remaining trials, one looked at tranexamic acid given prophylactically in the third stage of labour, and a final more recent study trialed tranexamic acid versus a placebo in women who were already experiencing a post partum haemorrhage. In all trials women also received uterotonics, as per the world health organisation recommendation7.

A compiled result of the reduction of blood loss achieved with the use of tranexamic acid was not applicable due to the fact that all studies used different doses, treatment regimes and timelines for documenting the degree of haemorrhage. However, individually all studies displayed a statistically significant reduction in blood loss after delivery.

## III. Prophylactic use in Cesarean Section

The largest randomized controlled trial, by Abdul-Aleem8 included 740 women, 373 of who received 1 gram of tranexamic acid intravenously 10 minutes prior to elective cesarean section. The mean total blood loss was 241.6ml in the tranexamic acid group, compared to 510.0 ml in the control group.

Goswami9 demonstrated a dose dependent relationship, with the mean total blood loss at cesarean section 527.17 ml in the control group, 376.83 ml in patients who received 10mg/kg tranexamic acid prior to cesarean and 261.17ml in those who received 15mg/kg.

The remaining studies determined a reduction in blood loss between 375.78ml and 62.5ml with the preoperative administration of tranexamic acid.10-16

## IV. Management of Post Partum Haemorrhage

Ducloy-Bouthors17 is the only randomized controlled trial that looks at using tranexamic acid as a treatment for women diagnosed with postpartum haemorrhage, rather than as a preventative measure. This is the most relevant study to date. With 144 women in the study the cohort was relatively small, but adequately powered to achieve significant results. These women had already had a postpartum haemorrhage of greater than or equal to 800ml at the time of randomization. Based on success in cardiac and orthopedic surgery, a high dose of 4grams of tranexamic acid over 1 hour, followed by 1gram/hour over 6hours was administered. Blood loss was measured at specified intervals from the time of randomization up until 6hours later. The control group had a median blood loss of 221ml compared to the group receiving tranexamic acid, which had a median blood loss of 173ml.

Throughout all seven trials there wasa trend towardreduced requirement for blood transfusion and further intervention when tranexamic acid was used, however these outcomes did not reach statistical significance.

## V. Adverse Events

Mild transient side effects, most commonly nausea, were reported with greater frequency among participants who had received treatment with tranexamic acid. There were no reports of deep vein thrombosis in any studies. Two patients in the tranexamic acid arm of the Ducloy-Bouthers17 trial developed superficial thrombosis at the site of the venous catheter, however one patient who did not receive the medication was diagnosed with the same condition. None of the studies reported side effects of clinical or statistical significance. A review of the use of tranexamic acid in surgery did not demonstrate an increased risk of thromboembolic events. Despite these findings, it would be imprudent to use tranexamic acid in patients with history of thrombosis or other risk factor that would preclude the use of antifibrinolytics in normal practice18.

Tranexamic acid crosses the placenta, which in theory may have some impact on the unborn baby if it is given prior to cesarean section, but obviously is not relevant if used as a treatment for post partum haemorrhage. It is excreted in very small amounts in breast milk, but to date no adverse events in breastfed babies have been reported.

## VI. Discussion

The available evidence for the use of tranexamic acid in postpartum haemorrhage remains limited, with the majority of the data of poor quality. However, support is mounting and the outcomes of all studies to date are cohesive in the finding that tranexamic acid does significantly reduce blood loss post partum. At this time, doses other than 1 gram intravenously, followed by a further 1gram if bleeding does not cease are not well supported. There is not yet enough evidence to support the routine use of tranexamic acid, or any suggestion that it may be used instead of traditional interventions including uterotonics.

A large study, the WOMAN trial (World Maternal Antifibrinolytic Trial) is currently being undertaken, and will hopefully provide stronger evidence for the use of tranexamic acid in clinically diagnosed postpartum haemorrhage19. The mediation is also being used with increasing frequency in other gynecological and obstetric conditions including bleeding after LLETZ and cone biopsy of the cervix, and in antepartum haemorrhage due to placenta praevia or diagnosed placental edge bleeds. More evidence is required to support the routine use of tranexamic acid in these conditions.

Situations in which post partum haemorrhage is ongoing after first line interventions, in cases where

bleeding may be due to factors other than uterine atony, and times when there may be a delay such as transferring a patient to theatre or to a larger centre for further treatment may be an appropriate instance to administer tranexamic acid.

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# Effect of Low Estrogen Level on Calcitriol and Other Bone Related Parameters in Postmenopausal Women

By Dr. Sangita Paneri, Dr. babli Yadav & Dr. Sumitra Yadav
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*Abstract-* Menopause is a major physiological event and is associated with metabolic changes. In order to study the changes associated with bone related parameters present study was planned. The study comprised 100 post menopausal women as study group and 100 ideal weight healthy premenopausal women as control. The blood samples were analyzed for following biochemical parameters serum calcium, phosphorus, alkaline phosphatase and calcitrol. Results revealed that the significant changes observed in calcium, phosphorus and calcitriol when compared to control.

*Keywords:* *postmenopause, calcitriol, bone related parameters.*

*GJMR-E Classification :* *NLMC Code: WJ 190*


*Strictly as per the compliance and regulations of:*

# Effect of Low Estrogen Level on Calcitriol and Other Bone Related Parameters in Postmenopausal Women

Dr. Sangita Paneri [α], Dr. babli Yadav [σ] & Dr. Sumitra Yadav [ρ]

*Abstract-* Menopause is a major physiological event and is associated with metabolic changes. In order to study the changes associated with bone related parameters present study was planned. The study comprised 100 post menopausal women as study group and 100 ideal weight healthy premenopausal women as control. The blood samples were analyzed for following biochemical parameters serum calcium, phosphorus, alkaline phosphatase and calcitrol. Results revealed that the significant changes observed in calcium, phosphorus and calcitriol when compared to control.

*Keywords: postmenopause, calcitriol, bone related parameters.*

## I. Introduction

Menopause is a normal event of women's life associated with hormonal changes these changes[1] may ideas to bone related problems. Abnormal mineral metabolism leads to bone related problem like osteoporosis, arthritis etc[2]. This has leads to hypothesis that can decrease calcium, phosphorus [3,4], which is responsible for bone related problem in post menopause [5,6]. Scanty work has been done in order to correlate low estrogen level with bone related parameters so present study was planned for evaluate effect of low estrogen level on calcitrol and other bone related parameters in postmenopausal women.

## II. Material and Methods

This study was conducted in the department of Biochemistry M.G.M. Medical college Indore from Jan 2013 to Dec 2013. A total of 200 subjects were taken among them 100 postmenopausal women taken as cases and 100 normal premenopausal women were taken as control subject. 2ml blood samples collected from each subject and samples were analyzed for serum calcium, phosphorus, alkaline phosphatase by using fully automatic Biochemistry analyzer and calcitriol was estimated by using radio immunoassay method [7].

## III. Statistical Analysis

Data were analysed using SPSS version 10 mean, S.D., paired and unpaired 't' test were calculated and significance was expressed by 'p' values.

*Table 1 :* Comparison of serum calcium, phosphorus, alkaline phosphatase and calcitriol level in postmenopausal women and control group

| S.No. | Parameters | Control group n=100 | Postmenopausal Women group n=100 | p value |
|---|---|---|---|---|
| 1 | Calcium (mg/dl) | 10.8 ±1.2 | 9 ± 1.6 | <0.05 |
| 2 | Phosphorus(mg/dl) | 3.5 ± 0.8 | 2.8 ± 0.6 | <0.05 |
| 3 | Alkaline phosphatase (U/L) | 52± 12 | 99 ± 26 | <0.05 |
| 4 | Calcitrol (pg/ml) | 29 ± 6.1 | 22.4 ±5.7 | <0.001 |

## IV. Results

The significant decrease observed in serum calcium and phosphorus level in postmenopausal women when compared to control.

The significant decrease is observed in serum vitamin D3 (calcitriol) level in postmenopausal women when compared with control.

The significant increase was observed in serum alkaline phosphatase level in postmenopausal women when compared to control.

## V. Discussion

Decrease level of calcium and phosphorus observed in postmenopausal women is due to low level of estrogen in postmenopaus leads to loss of calcium and phosphorus in urine [2]. A longitudinal study of bone related parameter by Nordin et al conclude the menopausal fall in calcium indicates a change in PTH

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set point and which leads to fall in GI absorption and tubular re-absorption of calcium and phosphorus. This is because of low activity of estrogen at these 2 sites [8]. Vitamin D3 level were found to be decreased in patient of osteoporosis. The women by increasing the intake of vitamin D3 can significantly reduce the bone loss and improve net bone density [8,9]. In the studies on hypervitaminosis D[6] and impaired vitamin D metabolism in post menopausal women shows low serum calcium was found to be significant univeriate predictor of hypovitaminosis D[10,11].

In present study significant correlation was observed between serum calcium, phosphorus, ALP level, and vitamin D level. A general awareness among the people is required to stress the importance of supplementary calcium with vitamin D. Preparation of intake of diets rich in calcium and vitamin D will be helpful to minimize the chances of osteoporosis and progression of osteoporosis in postmenopausal women.

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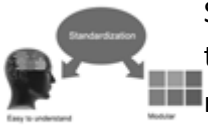


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**(A) (I) First, register yourself using top right corner of Home page then Login. If you are already registered, then login using your username and password.**

**(II) Choose corresponding Journal.**

**(III) Click 'Submit Manuscript'. Fill required information and Upload the paper.**

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# Preferred Author Guidelines

**MANUSCRIPT STYLE INSTRUCTION (Must be strictly followed)**

Page Size: 8.27" X 11'"

- Left Margin: 0.65
- Right Margin: 0.65
- Top Margin: 0.75
- Bottom Margin: 0.75
- Font type of all text should be Swis 721 Lt BT.
- Paper Title should be of Font Size 24 with one Column section.
- Author Name in Font Size of 11 with one column as of Title.
- Abstract Font size of 9 Bold, "Abstract" word in Italic Bold.
- Main Text: Font size 10 with justified two columns section
- Two Column with Equal Column with of 3.38 and Gaping of .2
- First Character must be three lines Drop capped.
- Paragraph before Spacing of 1 pt and After of 0 pt.
- Line Spacing of 1 pt
- Large Images must be in One Column
- Numbering of First Main Headings (Heading 1) must be in Roman Letters, Capital Letter, and Font Size of 10.
- Numbering of Second Main Headings (Heading 2) must be in Alphabets, Italic, and Font Size of 10.

**You can use your own standard format also.**
**Author Guidelines:**

1. General,

2. Ethical Guidelines,

3. Submission of Manuscripts,

4. Manuscript's Category,

5. Structure and Format of Manuscript,

6. After Acceptance.

**1. GENERAL**

Before submitting your research paper, one is advised to go through the details as mentioned in following heads. It will be beneficial, while peer reviewer justify your paper for publication.

**Scope**

The Global Journals Inc. (US) welcome the submission of original paper, review paper, survey article relevant to the all the streams of Philosophy and knowledge. The Global Journals Inc. (US) is parental platform for Global Journal of Computer Science and Technology, Researches in Engineering, Medical Research, Science Frontier Research, Human Social Science, Management, and Business organization. The choice of specific field can be done otherwise as following in Abstracting and Indexing Page on this Website. As the all Global

Journals Inc. (US) are being abstracted and indexed (in process) by most of the reputed organizations. Topics of only narrow interest will not be accepted unless they have wider potential or consequences.

**2. ETHICAL GUIDELINES**

Authors should follow the ethical guidelines as mentioned below for publication of research paper and research activities.

Papers are accepted on strict understanding that the material in whole or in part has not been, nor is being, considered for publication elsewhere. If the paper once accepted by Global Journals Inc. (US) and Editorial Board, will become the copyright of the Global Journals Inc. (US).

**Authorship: The authors and coauthors should have active contribution to conception design, analysis and interpretation of findings. They should critically review the contents and drafting of the paper. All should approve the final version of the paper before submission**

The Global Journals Inc. (US) follows the definition of authorship set up by the Global Academy of Research and Development. According to the Global Academy of R&D authorship, criteria must be based on:

1) Substantial contributions to conception and acquisition of data, analysis and interpretation of the findings.

2) Drafting the paper and revising it critically regarding important academic content.

3) Final approval of the version of the paper to be published.

All authors should have been credited according to their appropriate contribution in research activity and preparing paper. Contributors who do not match the criteria as authors may be mentioned under Acknowledgement.

Acknowledgements: Contributors to the research other than authors credited should be mentioned under acknowledgement. The specifications of the source of funding for the research if appropriate can be included. Suppliers of resources may be mentioned along with address.

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Approval for reproduction/modification of any information (including figures and tables) published elsewhere must be obtained by the authors/copyright holders before submission of the manuscript. Contributors (Authors) are responsible for any copyright fee involved.

**3. SUBMISSION OF MANUSCRIPTS**

Manuscripts should be uploaded via this online submission page. The online submission is most efficient method for submission of papers, as it enables rapid distribution of manuscripts and consequently speeds up the review procedure. It also enables authors to know the status of their own manuscripts by emailing us. Complete instructions for submitting a paper is available below.

Manuscript submission is a systematic procedure and little preparation is required beyond having all parts of your manuscript in a given format and a computer with an Internet connection and a Web browser. Full help and instructions are provided on-screen. As an author, you will be prompted for login and manuscript details as Field of Paper and then to upload your manuscript file(s) according to the instructions.

To avoid postal delays, all transaction is preferred by e-mail. A finished manuscript submission is confirmed by e-mail immediately and your paper enters the editorial process with no postal delays. When a conclusion is made about the publication of your paper by our Editorial Board, revisions can be submitted online with the same procedure, with an occasion to view and respond to all comments.

Complete support for both authors and co-author is provided.

**4. MANUSCRIPT'S CATEGORY**

Based on potential and nature, the manuscript can be categorized under the following heads:

Original research paper: Such papers are reports of high-level significant original research work.

Review papers: These are concise, significant but helpful and decisive topics for young researchers.

Research articles: These are handled with small investigation and applications

Research letters: The letters are small and concise comments on previously published matters.

**5.STRUCTURE AND FORMAT OF MANUSCRIPT**

The recommended size of original research paper is less than seven thousand words, review papers fewer than seven thousands words also.Preparation of research paper or how to write research paper, are major hurdle, while writing manuscript. The research articles and research letters should be fewer than three thousand words, the structure original research paper; sometime review paper should be as follows:

**Papers**: These are reports of significant research (typically less than 7000 words equivalent, including tables, figures, references), and comprise:

(a)Title should be relevant and commensurate with the theme of the paper.

(b) A brief Summary, "Abstract" (less than 150 words) containing the major results and conclusions.

(c) Up to ten keywords, that precisely identifies the paper's subject, purpose, and focus.

(d) An Introduction, giving necessary background excluding subheadings; objectives must be clearly declared.

(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, unless non-standard.

(f) Results should be presented concisely, by well-designed tables and/or figures; the same data may not be used in both; suitable statistical data should be given. All data must be obtained with attention to numerical detail in the planning stage. As reproduced design has been recognized to be important to experiments for a considerable time, the Editor has decided that any paper that appears not to have adequate numerical treatments of the data will be returned un-refereed;

(g) Discussion should cover the implications and consequences, not just recapitulating the results; conclusions should be summarizing.

(h) Brief Acknowledgements.

(i) References in the proper form.

Authors should very cautiously consider the preparation of papers to ensure that they communicate efficiently. Papers are much more likely to be accepted, if they are cautiously designed and laid out, contain few or no errors, are summarizing, and be conventional to the approach and instructions. They will in addition, be published with much less delays than those that require much technical and editorial correction.

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

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

**Format**

*Language: The language of publication is UK English. Authors, for whom English is a second language, must have their manuscript efficiently edited by an English-speaking person before submission to make sure that, the English is of high excellence. It is preferable, that manuscripts should be professionally edited.*

Standard Usage, Abbreviations, and Units: Spelling and hyphenation should be conventional to The Concise Oxford English Dictionary. Statistics and measurements should at all times be given in figures, e.g. 16 min, except for when the number begins a sentence. When the number does not refer to a unit of measurement it should be spelt in full unless, it is 160 or greater.

Abbreviations supposed to be used carefully. The abbreviated name or expression is supposed to be cited in full at first usage, followed by the conventional abbreviation in parentheses.

Metric SI units are supposed to generally be used excluding where they conflict with current practice or are confusing. For illustration, 1.4 l rather than 1.4 × 10-3 m3, or 4 mm somewhat than 4 × 10-3 m. Chemical formula and solutions must identify the form used, e.g. anhydrous or hydrated, and the concentration must be in clearly defined units. Common species names should be followed by underlines at the first mention. For following use the generic name should be constricted to a single letter, if it is clear.

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*Abstract, used in Original Papers and Reviews:*

Optimizing Abstract for Search Engines

Many researchers searching for information online will use search engines such as Google, Yahoo or similar. By optimizing your paper for search engines, you will amplify the chance of someone finding it. This in turn will make it more likely to be viewed and/or cited in a further work. Global Journals Inc. (US) have compiled these guidelines to facilitate you to maximize the web-friendliness of the most public part of your paper.

Key Words

A major linchpin in research work for the writing research paper is the keyword search, which one will employ to find both library and Internet resources.

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

Search engines for most searches, use Boolean searching, which is somewhat different from Internet searches. The Boolean search uses "operators," words (and, or, not, and near) that enable you to expand or narrow your affords. Tips for research paper while preparing research paper are very helpful guideline of research paper.

Choice of key words is first tool of tips to write research paper. Research paper writing is an art.A few tips for deciding as strategically as possible about keyword search:

- One should start brainstorming lists of possible keywords before even begin 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 research paper?" Then consider synonyms for the important words.
- It may take the discovery of only one relevant paper to let steer in the right keyword direction because in most databases, the keywords under which a research paper is abstracted are listed with the paper.
- One should avoid outdated words.

Keywords are the key that opens a door to research work sources. Keyword searching is an art in which researcher's skills are bound to improve with experience and time.

Numerical Methods: Numerical methods used should be clear and, where appropriate, supported by references.

*Acknowledgements: Please make these as concise as possible.*

References

References follow the Harvard scheme of referencing. References in the text should cite the authors' names followed by the time of their publication, unless there are three or more authors when simply the first author's name is quoted followed by et al. unpublished work has to only be cited where necessary, and only in the text. Copies of references in press in other journals have to be supplied with submitted typescripts. It is necessary that all citations and references be carefully checked before submission, as mistakes or omissions will cause delays.

References to information on the World Wide Web can be given, but only if the information is available without charge to readers on an official site. Wikipedia and Similar websites are not allowed where anyone can change the information. Authors will be asked to make available electronic copies of the cited information for inclusion on the Global Journals Inc. (US) homepage at the judgment of the Editorial Board.

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The Editorial Board and Global Journals Inc. (US) recommend the use of a tool such as Reference Manager for reference management and formatting.

Tables, Figures and Figure Legends

*Tables: Tables should be few in number, 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. Vertical lines should not be used.*

*Figures: Figures are supposed to be submitted as separate files. Always take in a citation in the text for each figure using Arabic numbers, e.g. Fig. 4. Artwork must be submitted online in electronic form by e-mailing them.*

Preparation of Electronic Figures for Publication

Even though low quality images are sufficient for review purposes, print publication requires high quality images to prevent the final product being blurred or fuzzy. Submit (or e-mail) EPS (line art) or TIFF (halftone/photographs) files only. MS PowerPoint and Word Graphics are unsuitable for printed pictures. Do not use pixel-oriented software. Scans (TIFF only) should have a resolution of at least 350 dpi (halftone) or 700 to 1100 dpi (line drawings) in relation to the imitation size. 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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*Figure Legends: Self-explanatory legends of all figures should be incorporated separately under the heading 'Legends to Figures'. In the full-text online edition of the journal, figure legends may possibly be truncated in abbreviated links to the full screen version. Therefore, the first 100 characters of any legend should notify the reader, about the key aspects of the figure.*

**6. AFTER ACCEPTANCE**

Upon approval of a paper for publication, the manuscript will be forwarded to the dean, who is responsible for the publication of the Global Journals Inc. (US).

**6.1 Proof Corrections**

The corresponding author will receive an e-mail alert containing a link to a website or will be attached. A working e-mail address must therefore be provided for the related author.

Acrobat Reader will be required in order to read this file. This software can be downloaded

(Free of charge) from the following website:

www.adobe.com/products/acrobat/readstep2.html. This will facilitate the file to be opened, read on screen, and printed out in order for any corrections to be added. Further instructions will be sent with the proof.

Proofs must be returned to the dean at dean@globaljournals.org within three days of receipt.

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## TECHNIQUES FOR WRITING A GOOD QUALITY RESEARCH PAPER:

**1. Choosing the topic:** In most cases, the topic is searched by the interest of author but it can be also suggested by the guides. You can have several topics and then you can judge that in which topic or subject you are finding yourself most comfortable. This can be done by asking several questions to yourself, like Will I be able to carry our search in this area? Will I find all necessary recourses to accomplish the search? Will I be able to find all information in this field area? If the answer of these types of questions will be "Yes" then you can choose that topic. In most of the cases, you may have to conduct the surveys and have to visit several places because this field is related to Computer Science and Information Technology. Also, you may have to do a lot of work to find all rise and falls regarding the various data of that subject. Sometimes, detailed information plays a vital role, instead of short information.

**2. Evaluators are human:** First thing to remember that evaluators are also human being. They are not only meant for rejecting a paper. They are here to evaluate your paper. So, present your Best.

**3. Think Like Evaluators:** If you are in a confusion or getting demotivated that your paper will be accepted by evaluators or not, then think and try to evaluate your paper like an Evaluator. Try to understand that what an evaluator wants in your research paper and automatically you will have your answer.

**4. 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.

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

**6. Use of computer is recommended:** As you are doing research in the field of Computer Science, then this point is quite obvious.

**7. Use right software:** Always use good quality software packages. If you are not capable to judge good software then you can lose quality of your paper unknowingly. There are various software programs available to help you, which you can get through Internet.

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**9. Use and get big pictures:** Always use encyclopedias, Wikipedia to get pictures so that you can go into the depth.

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

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

**12. Make all efforts:** Make all efforts to mention what you are going to write in your paper. That means always have a good start. Try to mention everything in introduction, that what is the need of a particular research paper. Polish your work by good skill of writing and always give an evaluator, what he wants.

**13. Have backups:** When you are going to do any important thing like making research paper, you should always have backup copies of it either in your computer or in paper. This will help you to not to lose any of your important.

**14. Produce good diagrams of your own:** Always try to include good charts or diagrams in your paper to improve quality. Using several and unnecessary diagrams will degrade the quality of your paper by creating "hotchpotch." So always, try to make and include those diagrams, which are made by your own to improve readability and understandability of your paper.

**15. Use of direct quotes:** When you do research relevant to literature, history or current affairs then use of quotes become essential but if study is relevant to science then use of quotes is not preferable.

**16. Use proper verb tense:** Use proper verb tenses in your paper. Use past tense, to present those events that happened. Use present tense to indicate events that are going on. Use future tense to indicate future happening events. Use of improper and wrong tenses will confuse the evaluator. Avoid the sentences that are incomplete.

**17. Never use online paper:** If you are getting any paper on Internet, then never use it as your research paper because it might be possible that evaluator has already seen it or maybe it is outdated version.

**18. Pick a good study spot:** To do your research studies always try to pick a spot, which is quiet. Every spot is not for studies. Spot that suits you choose it and proceed further.

**19. Know what you know:** Always try to know, what you know by making objectives. Else, you will be confused and cannot achieve your target.

**20. Use good quality grammar:** Always use a good quality grammar and use words that will throw positive impact on evaluator. Use of good quality grammar does not mean to use tough words, that for each word the evaluator has to go through dictionary. Do not start sentence with a conjunction. Do not fragment sentences. Eliminate one-word sentences. Ignore passive voice. Do not ever use a big word when a diminutive one would suffice. Verbs have to be in agreement with their subjects. Prepositions are not expressions to finish sentences with. It is incorrect to ever divide an infinitive. Avoid clichés like the disease. Also, always shun irritating alliteration. Use language that is simple and straight forward. put together a neat summary.

**21. 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 to your topic. You may also maintain your arguments with records.

**22. Never start in last minute:** Always start at right time and give enough time to research work. Leaving everything to the last minute will degrade your paper and spoil your work.

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

**24. Never copy others' work:** Never copy others' work and give it your name because if evaluator has seen it anywhere you will be in trouble.

**25. Take proper rest and food:** No matter how many hours you spend for your research activity, if you are not taking care of your health then all your efforts will be in vain. For a quality research, study is must, and this can be done by taking proper rest and food.

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

**27. Refresh your mind after intervals:** Try to give rest to your mind by listening to soft music or by sleeping in intervals. This will also improve your memory.

**28. Make colleagues:** Always try to make colleagues. No matter how sharper or intelligent you are, if you make colleagues you can have several ideas, which will be helpful for your research.

**29. Think technically:** Always think technically. If anything happens, then search its reasons, its benefits, and demerits.

**30. Think and then print:** When you will go to print your paper, notice that tables are not be split, headings are not detached from their descriptions, and page sequence is maintained.

**31. Adding unnecessary information:** Do not add unnecessary information, like, I have used MS Excel to draw graph. Do not add irrelevant and inappropriate material. These all will create superfluous. Foreign terminology and phrases are not apropos. One should NEVER take a broad view. Analogy in script is like feathers on a snake. Not at all use a large word when a very small one would be sufficient. Use words properly, regardless of how others use them. Remove quotations. Puns are for kids, not grunt readers. Amplification is a billion times of inferior quality than sarcasm.

**32. Never oversimplify everything:** To add material in your research paper, never go for oversimplification. This will definitely irritate the evaluator. Be more or less specific. Also too, by no means, ever use rhythmic redundancies. Contractions aren't essential and shouldn't be there used. Comparisons are as terrible as clichés. Give up ampersands and abbreviations, and so on. Remove commas, that are, not necessary. Parenthetical words however should be together with this in commas. Understatement is all the time the complete best way to put onward earth-shaking thoughts. Give a detailed literary review.

**33. Report concluded results:** Use concluded results. From raw data, filter the results and then conclude your studies based on measurements and observations taken. Significant figures and appropriate number of decimal places should be used. Parenthetical remarks are prohibitive. Proofread carefully at final stage. In the end give outline to your arguments. Spot out perspectives of further study of this subject. Justify your conclusion by at the bottom of them with sufficient justifications and examples.

**34. After 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 to 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 in 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 criterion for grading the final paper by peer-reviewers.

**Final Points:**

A purpose of organizing a research paper is to let people to interpret your effort selectively. The journal requires the following sections, submitted in the order listed, each section to start on a new page.

The introduction will be compiled from reference matter and will reflect the design processes or outline of basis that direct you to make study. As you will carry out the process of study, the method and process section will be constructed as like that. The result segment will show related statistics in nearly sequential order and will direct the reviewers next to the similar intellectual paths throughout the data that you took to carry out your study. The discussion section will provide understanding of the data and projections as to the implication of the results. The use of good quality references all through the paper will give the effort trustworthiness by representing an alertness of 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 the progression.

**General style:**

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

To make a paper clear

· Adhere to recommended page limits

Mistakes to evade

- Insertion a title at the foot of a page with the subsequent text on the next page
- Separating a table/chart or figure - impound each figure/table to a single page
- Submitting a manuscript with pages out of sequence

In every sections of your document

· Use standard writing style including articles ("a", "the," etc.)

· Keep on paying attention on the research topic of the paper

· Use paragraphs to split each significant point (excluding for the abstract)

· Align the primary line of each section

· Present your points in sound order

· Use present tense to report well accepted

· Use past tense to describe specific results

· Shun familiar wording, don't address the reviewer directly, and don't use slang, slang language, or superlatives

· Shun use of extra pictures - include only those figures essential to presenting results

**Title Page:**

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

**Abstract:**

The summary should be two hundred words or less. It should briefly and clearly explain the key findings reported in the manuscript--must have precise statistics. It should not have abnormal acronyms or abbreviations. It should be logical in itself. Shun citing 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 approach 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. Yet, use comprehensive sentences and do not let go readability for briefness. You can maintain it succinct by phrasing sentences so that they provide more than 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 maintain the initial two items to no more than one ruling each.

- Reason of the study - 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 quantitative data; results of any numerical analysis should be reported
- Significant conclusions or questions that track from the research(es)

Approach:

- Single section, and succinct
- As a outline of job done, it is always written in past tense
- A conceptual should situate on its own, and not submit to any other part of the paper such as a form or table
- Center on shortening results - bound background information to a verdict or two, if completely necessary
- What you account in an conceptual must be regular with what you reported in the manuscript
- Exact spelling, clearness 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 to comprehend and calculate the purpose of your study without having to submit to other works. The basis for the study should be offered. Give most important references but shun difficult to make a comprehensive appraisal of the topic. In the introduction, describe the problem visibly. If the problem is not acknowledged in a logical, reasonable way, the reviewer will have no attention in your result. Speak in common terms about techniques used to explain the problem, if needed, but do not present any particulars about the protocols here. Following approach can create a valuable beginning:

- Explain the value (significance) of the study
- Shield the model - why did you employ this particular system or method? What is its compensation? You strength remark on its appropriateness from a abstract point of vision as well as point out sensible reasons for using it.
- Present a justification. Status your particular theory (es) or aim(s), and describe the logic that led you to choose them.
- Very for a short time explain the tentative propose and how it skilled 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 with every section. If you make the four points listed above, you will need a least of four paragraphs.

- Present surroundings information only as desirable in order hold up a situation. The reviewer does not desire to read the whole thing you know about a topic.
- Shape the theory/purpose 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 sound written Procedures segment allows a capable scientist to replacement 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 for the least amount of information that would permit another capable scientist to spare 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 object, mention the specific item describing a way but draw the basic principle while stating the situation. The purpose is to text 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:

- Explain materials individually only if the study is so complex that it saves liberty this way.
- Embrace particular materials, and any tools or provisions that are not frequently found in laboratories.
- Do not take in frequently found.
- If use of a definite type of tools.
- Materials may be reported in a part section or else they may be recognized along with your measures.

Methods:

- Report the method (not 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 - details how procedures were completed not how they were exclusively performed on a particular day.
- If well known procedures were used, account the procedure by name, possibly with reference, and that's all.

Approach:

- It is embarrassed or not possible to use vigorous voice when documenting methods with no using first person, which would focus the reviewer's interest on the researcher rather than the job. As a result when script up the methods most authors use third person passive voice.
- Use standard style in this and in every other part of the paper - avoid familiar lists, and use full sentences.

What to keep away from

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

**Results:**

The principle of a results segment is to present and demonstrate your conclusion. Create this part a 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. Carry on to be to the point, by means of statistics and tables, if suitable, to present consequences most efficiently.You must obviously differentiate material that would usually be incorporated in a study editorial from any unprocessed data or additional appendix matter that would not be available. In fact, such matter should not be submitted at all except requested by the instructor.

Content

- Sum up your conclusion in text and demonstrate them, if suitable, with figures and tables.
- In manuscript, explain each of your consequences, point the reader to remarks that are most appropriate.
- Present a background, such as by describing the question that was addressed by creation an exacting study.
- Explain results of control experiments and comprise 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 in manuscript form.

What to stay away from

- Do not discuss or infer your outcome, report surroundings information, or try to explain anything.
- Not at all, take in raw data or intermediate calculations in a research manuscript.
- Do not present the similar data more than once.
- Manuscript should complement any figures or tables, not duplicate the identical information.
- Never confuse figures with tables - there is a difference.

Approach

- As forever, use past tense when you submit to 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 part.

Figures and tables

- If you put figures and tables at the end of the details, make certain that they are visibly distinguished from any attach appendix materials, such as raw facts
- Despite of position, each figure must be numbered one after the other and complete with subtitle
- In spite of position, each table must be titled, numbered one after the other and complete with heading
- All figure and table must be adequately complete that it could situate on its own, divide from text

**Discussion:**

The Discussion is expected the trickiest segment to write and describe. A lot of papers submitted for journal are discarded based on problems with the Discussion. There is no head of state for how long a 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 implication of the study. The purpose here is to offer an understanding of your results and hold up for all of your conclusions, using facts from your research and generally accepted information, if suitable. The implication of result should be visibly 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 with prospect, and let it drop at that.

- Make a decision if each premise is supported, 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 the experiment might be personalized to accomplish a new idea.
- Give details all of your remarks as much as possible, focus on mechanisms.
- Make a decision if the tentative design sufficiently addressed the theory, and whether or not it was correctly restricted.
- Try to present substitute explanations if sensible alternatives be present.
- One 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 available information
- Submit to work done by specific persons (including you) in past tense.
- Submit to 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 |
| ***Methods and Procedures*** | Clear and to the point with well arranged paragraph, precision and accuracy of facts and figures, well organized subheads | Difficult to comprehend with embarrassed text, too much explanation but completed | Incorrect and unorganized structure with hazy meaning |
| ***Result*** | Well organized, Clear and specific, Correct units with precision, correct data, well structuring of paragraph, no grammar and spelling mistake | Complete and embarrassed text, difficult to comprehend | Irregular format with wrong facts and figures |
| ***Discussion*** | Well organized, meaningful specification, sound conclusion, logical and concise explanation, highly structured paragraph reference cited | Wordy, unclear conclusion, spurious | Conclusion is not cited, unorganized, difficult to comprehend |
| ***References*** | Complete and correct format, well organized | Beside the point, Incomplete | Wrong format and structuring |

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