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Abnormal Uterine Bleeding

Combined Factor V and Factor VIII

Highlights

Maternal and Perinatal Outcome

Role of Anemia and Thrombotic Risk Factors

Discovering Thoughts, Inventing Future

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Case Report on Management of Combined Factor V and Factor VIII Deficiency during Pregnancy

By Dr. Kirti Solanki, Dr. Swati Kochar, Dr. Shweta Choudhary,
Dr. Priyanka Gaur & Dr. Krishna

Abstract- Combined factor V and factor VIII deficiency (CF5F8D) is a rare autosomal recessive disorder associated with mild to moderate risk of bleeding tendency. These patients have an increased risk of bleeding after surgical procedures. Pregnant women are at increased risk of having a miscarriage, placental abruption, or post partum hemorrhage. Management of these patients requires the replacement of deficient factors. We are reporting a case of management of a 31-year old second gravida female with combined factor V and factor VIII deficiency, who was transfused with fresh frozen plasma before and during labor to prevent bleeding episodes.

Keywords: *autosomal recessive, bleeding disorder, post partum hemorrhage, fresh frozen plasma.*

GJMR-E Classification: *NLMC Code: WQ 240*



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Case Report on Management of Combined Factor V and Factor VIII Deficiency during Pregnancy

Dr. Kirti Solanki ^α, Dr. Swati Kochar ^σ, Dr. Shweta Choudhary ^ρ, Dr. Priyanka Gaur ^ω & Dr. Krishna [¥]

Abstract- Combined factor V and factor VIII deficiency (CF5F8D) is a rare autosomal recessive disorder associated with mild to moderate risk of bleeding tendency. These patients have an increased risk of bleeding after surgical procedures. Pregnant women are at increased risk of having a miscarriage, placental abruption, or post partum hemorrhage. Management of these patients requires the replacement of deficient factors. We are reporting a case of management of a 31-year old second gravida female with combined factor V and factor VIII deficiency, who was transfused with fresh frozen plasma before and during labor to prevent bleeding episodes.

Keywords: autosomal recessive, bleeding disorder, post partum hemorrhage, fresh frozen plasma.

I. INTRODUCTION

Combined factor V and factor VIII deficiency (CF5F8D) is a rare autosomal recessive disorder requiring both parents to carry the defective gene to transfer the disease. Its prevalence is 1 per 1000000 in the general population. Prevalence is higher in areas where consanguineous marriages are common^{1,2}. It is associated with mild to moderate risk of bleeding tendency. Mild bleeding symptoms include easy bruising, epistaxis, gum bleeding, etc. These persons are at high risk of bleeding after surgery, dental extraction, and trauma. Women with combined factor V and factor VIII deficiency are at increased risk of having menorrhagia and post partum hemorrhage.¹ Pregnancy is itself a risk factor for deranged coagulation, and post partum hemorrhage is an important cause of maternal mortality and morbidity. Hence in obstetrical practice multidisciplinary approach to a patient with bleeding disorders and coagulation factor deficiency is of significant importance. There have been several literatures that document the risk of miscarriage and placental abruption resulting in fetal loss or premature delivery in women with bleeding disorders. There is fewer data available on the optimal management of women with CF5F8D with term pregnancy. The aim of this paper is to report a case of successful pregnancy outcomes in a woman with a combined deficiency of Factor V and Factor VIII.

II. CASE REPORT

We here report a case of successful pregnancy outcomes in a young woman with combined factor V and factor VIII deficiency. A 31-year old female was admitted to labor room of the obstetrics and gynecological department of Sardar Patel medical college at 38 weeks of gestation for delivery. She had previous one normal vaginal delivery three years back. At the time of admission the patient was hemodynamically stable. At two months of amenorrhea, she consulted a gynecologist. Her routine investigation was done including complete blood count, liver function test, renal function test, blood grouping, and ultrasonography. All blood investigations were normal. She had history of combined factor V and factor VIII deficiency, in view of which her prothrombin time, INR, and APTT was assessed. She had prolonged PT (14.90 sec) and APTT(88.20 sec) patient control ratio being(1.41) and raised INR(1.49). She was also tested for functional factor V and functional factor VIII levels and found to be deficient in both, the levels being less than 3% and 6%, respectively. She was counseled about the maternal and fetal risks and probable pregnancy outcomes. Patient was regular regarding her antenatal visits timely. Opinion from a hematologist was also taken. Regular monitoring of PT and APTT was performed throughout pregnancy. At 38 weeks, she was admitted for delivery after consulting a hematologist. Patient's routine investigations, including coagulation profile PT, APTT & INR, were performed. Her Hb was-10.8gm% platelet was-155000/mm³. The bleeding time was 2.40sec, and the clotting time was 5.10 sec. Her PT(20.50 sec) and APTT(64.00sec) were prolonged, and her INR was 1.47. In view of deranged coagulation parameters, patient was transfused with 150ml/kg of fresh frozen plasma before induction of labor and during labor. After 18 hours of induction, she gave birth to a healthy baby girl of 2.8 kg. Her third stage of labor was actively managed. Her puerperium period was uneventful.

III. DISCUSSION

Combined Factor 5 and Factor 8 deficiency was first described by Oeri et al. in 1954.³ It is a rare autosomal recessive disorder, characterized by

Author α: e-mail: solanki.kirti100@gmail.com

concomitantly low levels (usually between 5% and 20%) of the two coagulation factors, Factor V and Factor VIII.⁴ Mutations in two genes, lectin mannose-binding protein 1 (LMAN1), and multiple coagulation factor deficiency 2 (MCFD2) are identified as the cause of CF5F8D. These genes encode for proteins involved in the intracellular transport of Factor V and Factor VIII.⁵ Its prevalence is 1 per 1000000 in the general population, which is higher in consanguineous marriages. It is associated with a mild to moderate bleeding tendency. CF5F8D patients are characterized by normal platelet count and bleeding time and prolonging both prothrombin time (PT) and partial thromboplastin time tests (PTT).⁶ Specific assays of FV and FVIII coagulant activity are necessary to evaluate the residual FV and FVIII coagulant activity.

During pregnancy, the physiological changes in the hemostatic system tend to improve the inherited bleeding disorders. Pregnancy is accompanied by increased concentrations of fibrinogen, FVII, FVIII, FX and, von Willebrand factor, while FII, FV and, FIX are relatively unchanged.^{7,8} The active, unbound form of free protein S is decreased during pregnancy and, plasminogen activator inhibitor type 1 (PAI-1) levels are increased.⁷ All of these changes lead to the hypercoagulable state of pregnancy, and improve hemostasis in women with rare bleeding disorders. Despite these changes, women with factor deficiencies do not achieve the same factor levels as those women without factor deficiencies.^{9,10} And these women remain at high risk of bleeding complications. In view of general recommendations for the management of bleeding disorders in pregnancy, affected women should be managed by an obstetric unit along with a hemophilia center. CF5F8D patients usually do not require regular prophylaxis. Any surgical intervention requires the replacement of factors. The plasma half-life of factors is FV: 36 h; FVIII: 10–14 h. FV concentrates are not available and are not present in cryoprecipitate or prothrombin complex concentrates; replacement of FV can be achieved only through the use of fresh frozen plasma (FFP), preferably with virus-inactivated plasma. For FVIII replacement, many products are available, including FFP, plasma-derived concentrates, or recombinant FVIII (rFVIII). Surgical procedures like vaginal delivery or cesarean delivery should be addressed by administering factor V and factor VIII 30 min before surgery and then every 12 h to maintain FVIII levels above 50 IU dL and FV levels above 25 IU dL until wound healing is established.¹¹

To women with inherited bleeding disorders, pregnancy and childbirth present a major challenge. All women should be managed by a multidisciplinary team in a center where the expertise, laboratory support, and factor treatment required to provide care to these patients are available at all times. Additional reports are needed for establishing optimal guidelines for

hemorrhagic, invasive, and surgical procedures in individuals with combined factors V and VIII deficiency.

IV. CONCLUSION

A combined FV and FVIII deficiency is one of the rarest coagulation factor deficiencies. During pregnancy, this combined deficiency could have adverse consequences by causing uncontrollable bleeding with a risk of maternal death. The management must thus be multidisciplinary and should begin with an early assessment of hemorrhagic risk leading to a written FV and FVIII substitution protocol tailored to each parturient.

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Using PALM-COEIN FIGO Classification for Categorization of Patients with Abnormal Uterine Bleeding

By Foram P. Acharya, Babulal S. Patel, Akshay C. Shah & Shashwat K. Jani

Abstract- Background: Abnormal uterine bleeding is one of the most common problems of the women of reproductive age group leading to increased number of hospital visits. For describing and categorizing the common problem of abnormal uterine bleeding in these women, an alternative classification system polyp, adenomyosis, leiomyoma, malignancy and hyperplasia, coagulopathy, ovulatory dysfunction, endometrial, iatrogenic, and not yet classified, known by the acronym PALM-COEIN was developed by FIGO.

Methods: This is a retrospective study on 150 patients of abnormal uterine bleeding to categorize them on the basis of PALM-COEIN classification. Patient were grouped under these categories after detailed history, examination, investigations and histopathological reports.

Keywords: abnormal uterine bleeding, adenomyosis, leiomyoma, ovulatory dysfunction, PALM-COEIN, Polyp.

GJMR-E Classification: NLMC Code: WQ 240



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Using PALM-COEIN FIGO Classification for Categorization of Patients with Abnormal Uterine Bleeding

Foram P. Acharya ^α, Babulal S. Patel ^ο, Akshay C. Shah ^ρ & Shashwat K. Jani ^ω

Abstract- Background: Abnormal uterine bleeding is one of the most common problems of the women of reproductive age group leading to increased number of hospital visits. For describing and categorizing the common problem of abnormal uterine bleeding in these women, an alternative classification system polyp, adenomyosis, leiomyoma, malignancy and hyperplasia, coagulopathy, ovulatory dysfunction, endometrial, iatrogenic, and not yet classified, known by the acronym PALM-COEIN was developed by FIGO.

Methods: This is a retrospective study on 150 patients of abnormal uterine bleeding to categorize them on the basis of PALM-COEIN classification. Patient were grouped under these categories after detailed history, examination, investigations and histopathological reports.

Results: Ovulatory dysfunction was the most common cause of AUB in patients presenting to the gynecology outpatient department (n=43, 28.67%). It was followed by leiomyoma (n=35, 23.33%) and endometrial causes (n=30, 20%). They constitute the top 3 causes of AUB. Adenomyosis (n=20, 13.33%), not classified (n=10, 6.67%), iatrogenic (n=6, 4%), polyp (n=3, 2%), coagulopathy (n=2, 1.33%) and malignancy (n=1, 0.67%) contributing least to the PALM-COEIN classification as an etiology for AUB.

Conclusions: PALM-COEIN classification is a universally accepted and reliable method of knowing exact etiology following investigations, so that proper treatment can be done for AUB.

Keywords: abnormal uterine bleeding, adenomyosis, leiomyoma, ovulatory dysfunction, PALM-COEIN, Polyp.

I. INTRODUCTION

Abnormal uterine bleeding (AUB) may be acute or chronic and is defined as bleeding from the uterine corpus that is abnormal in regularity, volume, frequency or duration and occurs in the absence of pregnancy.^{1,2}

Abnormal uterine bleeding is one of the most common problems of the women of reproductive age group leading to increased number of hospital visits.

For describing and categorizing the common problem of abnormal uterine bleeding in these women, an alternative classification system polyp, adenomyosis, leiomyoma, malignancy and hyperplasia, coagulopathy, ovulatory dysfunction, endometrial, iatrogenic, and not yet classified, known by the acronym PALM-COEIN was developed by FIGO.

PALM-COEIN, was published in 2011 by the International Federation of Gynecology and Obstetrics and adopted by the American College of Obstetricians and Gynecologists.³

The PALM-COEIN system uses bleeding pattern and etiology in order to classify uterine bleeding. The overarching term AUB is paired descriptive terms to denote bleeding patterns associated with AUB, such as heavy menstrual bleeding (instead of menorrhagia) and intermenstrual bleeding (instead of metrorrhagia).³

The term dysfunctional uterine bleeding - often used synonymously with AUB in the literature to indicate AUB for which there was no systemic or locally definable structural cause - is not part of the PALM-COEIN system, and discontinuation of its use is recommended.³

Thus, this classification system helps us in identifying the etiology of uterine bleeding which in turn helps us in managing these patients. In symptomatic women, there can be more than one cause for the same. So, precise diagnosis and classification helps us in better management.

II. METHODS

The present study is a retrospective observational study conducted at the Obstetrics and Gynecology Department of Smt. NHL Municipal Medical College and its affiliated hospitals (SVPIMSR and Sheth V. S. General Hospital & Chinai Maternity Home), from 16th December, 2019 to 16th July, 2020. We studied 150 women for this, who met the inclusion criteria.

a) Inclusion criteria

- Women belonging to reproductive age group, between menarche to menopause.
- History of unpredictable, irregular menses or excessive bleeding for prolonged duration.
- Increased frequency of menses and intermenstrual bleeding for at least 3 months of duration.

Corresponding Author α: Department of Obstetrics and Gynecology, Smt. NHL Municipal Medical College, SVPIMSR, Ellisbridge, Ahmedabad, Gujarat, India. e-mail: foram95@yahoo.com

Author ο ρ ω: Department of Obstetrics and Gynecology, Smt. NHL Municipal Medical College, SVPIMSR, Ahmedabad.

b) *Exclusion criteria*

- Vaginal bleeding because of cervical cause
- Abnormal bleeding in antenatal patients.

After informed consent, we took detailed history including drug history and examined the patient, along with necessary blood investigations like CBC, Coagulation profile, S. TSH, S. Prolactin etc. and pelvic ultrasonography was done to rule out any structural abnormalities. We obtained the histopathology reports of endometrial biopsy or hysterectomy specimen wherever needed. The possible causes were identified based on examination and investigations, and patients categorized according to PALM-COEIN classification. Polyp, adenomyosis and leiomyoma were identified after per speculum and per vaginal examination followed by ultrasound and were categorized under AUB-P, AUB-A and AUB-L respectively. AUB-M category included patients with bleeding because of endometrial carcinoma diagnosed on the basis of histopathological report of endometrial biopsy. These patients were referred to other center for further management. AUB-C category included the patients taking any form of anticoagulant or with known history of coagulation defects since a younger age. AUB-O included bleeding due to ovarian dysfunction, with irregular timing or unpredictable bleeding patterns with variable amounts of bleeding. AUB-E was used for abnormal bleeding occurring in cyclical and predictable pattern usually suggestive of ovulatory cycle and no other cause was identifies. AUB-I included patients with intrauterine devices (inert or medicated) or having history of gonadal steroid intake in the preceding 3 months. Women not fitting into any category (Endometritis, AV Malformation) were put under not yet classified category i.e. AUB-N.4-6.

c) *Statistical analysis*

Data was analyzed and descriptive statistics were presented as frequencies and percentages.

III. RESULTS

We included 150 participants who fulfilled all the inclusion criteria in this study. All these cases were placed in the nine categories of the PALM-COEIN classification.

Table 1: Age distribution of study population

| Age group (years) | Overall, n=150 (%) |
|-------------------|--------------------|
| <20 years | 4 (2.67) |
| 20-29 years | 11 (7.33) |
| 30-39 years | 58 (38.67) |
| 40-49 years | 69 (46) |
| >49 | 8 (5.33) |

Age group of 40-49 years (n=69, 46%) (Table 1) was the most common age group. With heavy menstrual bleeding (n=74, 49.33%) (Table 2) being the most common complaint.

Table 2: Distribution of study population based on presenting complaint

| Complaint | n=150 (%) |
|--------------------------|------------|
| Heavy menstrual bleeding | 74 (49.33) |
| Irregular bleeding | 35 (23.33) |
| Intermenstrual spotting | 9 (6) |
| Frequent menses | 32 (21.33) |

After classifying the patients according to PALM-COEIN classification, it was found that Ovulatory dysfunction was the most common cause of AUB in patients presenting to the gynecology outpatient department (n=43, 28.67%). It was followed by leiomyoma (n=35, 23.33%) and endometrial causes (n=30, 20%) and were the top three etiologies for AUB respectively. Adenomyosis (n=20, 13.33%), not classified (n=10, 6.67%), iatrogenic (n=6, 4%), polyp (n=3, 2%), coagulopathy (n=2, 1.33%) and malignancy (n=1, 0.67%) contributing least to the PALM-COEIN classification as an etiology for AUB (Table 3).

Table 3: Distribution of study population based on PALM-COEIN classification

| PALM-COEIN | n=150 (%) |
|-----------------------|------------|
| Polyp | 3 (2) |
| Adenomyosis | 20 (13.33) |
| Leiomyoma | 35 (23.33) |
| Malignancy | 1 (0.67) |
| Coagulopathy | 2 (1.33) |
| Ovulatory dysfunction | 43 (28.67) |
| Endometrial | 30 (20) |
| Iatrogenic | 6 (4) |
| Not known | 10 (6.67) |

IV. DISCUSSION

According to the study done by Qureshi and Yusuf, maximum patients of AUB were classified under leiomyoma category, the number being 25% followed by ovulatory dysfunction (24%).⁷ According to a study done by Gouri et al, maximum number of patients were categorized under ovulatory dysfunction (27%) followed by leiomyoma (24.67%). Also, in a study done by Tater A, Jain P & Sharma KN, maximum patients of AUB were seen in Ovulatory dysfunction (30%) followed by leiomyoma (24%).⁸ Similarly, in the present study also, ovulatory dysfunction (n=43, 28.67%) was found to be the most common cause of AUB followed by leiomyoma (n=35, 23.33%).

Specific management of various categories of PALM COEIN classification like AUB-P includes resection of polyp, AUB-A includes hysterectomy or adenomyomectomy (not frequently preferred), AUB-M includes surgery +/- adjuvant treatment, or if surgery is not possible, it can be managed using high dose progesterone or palliation (including radiotherapy), AUB-C includes using Tranaxemic acid, AUB-O can be

managed by lifestyle modification or specific management of hyperprolactinemia using cabergoline or hypothyroidism using levothyroxine. Antibiotics can be given for endometritis and embolization can be done for AV malformations.

There are various previous studies done by Khrouf et al, Munro et al, Madhra et al, Bahamondes and Ali. Which categorize patients of AUB according to the FIGO PALM-COEIN classification.3,9-11

In almost all the previous studies, ovulatory dysfunction and leiomyoma contribute the most for abnormal uterine bleeding.

V. CONCLUSION

PALM-COEIN classification is a universally accepted and reliable method of knowing exact etiology following investigations, so that proper treatment can be done for AUB. This classification may need periodic modification with advancement of investigative modalities. Management is decided according to the cause of uterine bleeding, and this classification makes it easier for deciding upon the management of given cause.

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The Role of Anemia and Thrombotic Risk Factors in Pregnancy Complications

By Lidiya Buzyan

Abstract- In a case-control study of 454 pregnancy and delivery cases, women with and without thrombotic risk factors showed different effects of anemia on pregnancy. In women with risk factors and anemia, miscarriage was significantly less common than in patients without anemia. High hemoglobin levels in the 1st trimester were associated with an increased risk of preeclampsia in the same group. Middle and severe anemia was associated with preterm birth, and also with placental insufficiency in women with thrombotic risk factors. Iron supplementation for mild anemia without confirmed iron deficiency may trigger urinary tract infections in pregnant women.

Keywords: *анемия, беременность, преэклампсия, невынашивание.*

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The Role of Anemia and Thrombotic Risk Factors in Pregnancy Complications

РОЛЬ АНЕМИИ И ФАКТОРОВ ТРОМБОТИЧЕСКОГО РИСКА В РЕАЛИЗАЦИИ ГЕСТАЦИОННЫХ ОСЛОЖНЕНИЙ

Lidiya Buzyan

Аннотация- В исследовании "случай-контроль", включившем 454 истории беременности и родов, женщины с факторами тромботического риска и без них демонстрировали отличающиеся эффекты анемии на течение беременности. У женщин с факторами риска и анемией значимо реже наблюдалось невынашивание, чем у пациенток без анемии. Высокий уровень гемоглобина в 1 триместре ассоциирован с повышенным риском преэклампсии в этой же группе. Анемия средней и тяжелой степени ассоциирована с преждевременными родами, а у женщин с факторами тромботического риска также и с плацентарной недостаточностью. Назначение препаратов железа при легкой анемии без подтвержденного дефицита железа, возможно, провоцирует у беременных инфекции мочевыводящих путей.

Abstract- In a case-control study of 454 pregnancy and delivery cases, women with and without thrombotic risk factors showed different effects of anemia on pregnancy. In women with risk factors and anemia, miscarriage was significantly less common than in patients without anemia. High hemoglobin levels in the 1st trimester were associated with an increased risk of preeclampsia in the same group. Middle and severe anemia was associated with preterm birth, and also with placental insufficiency in women with thrombotic risk factors. Iron supplementation for mild anemia without confirmed iron deficiency may trigger urinary tract infections in pregnant women.

Ключевые слова: анемия, беременность, преэклампсия, невынашивание.

Актуальность

Традиционно анемия во время беременности (снижение концентрации гемоглобина до 110 г/л и ниже) считается патологическим состоянием, ассоциированным с преждевременными родами, плацентарной недостаточностью с задержкой роста и гипоксией плода, а также, по некоторым данным, увеличивающим частоту возникновения и тяжесть течения преэклампсии. При этом в рутинной медицинской практике тип анемии у беременной зачастую не дифференцируется, диагностика ограничивается исследованием общего анализа крови, и все случаи снижения концентрации гемоглобина автоматически приравниваются к железодефицитному состоянию и подлежат лечению препаратами железа.

Между тем, снижение концентрации гемоглобина во время беременности происходит вследствие физиологической гемодилюции, а железо, кроме того, потребляется тканями плаценты и плода. Тканевые резервы железа велики, в организме предусмотрены системы реутилизации железа из разрушенных эритроцитов, поэтому для развития его истинного дефицита требуется продолжительное время – порядка нескольких лет[1].

Кроме того, на практике зачастую недооцениваются потенциальные побочные и токсические эффекты чрезмерного насыщения организма железом – активация перекисного окисления липидов, окислительный стресс, а также стимуляция роста патогенной микрофлоры, что, в частности, приводит к увеличению частоты и тяжести течения инфекций мочевыводящих путей у беременных[3].

Физиологическая гемодилюция предотвращает развитие тяжелого ДВС-синдрома в родах, при оперативных вмешательствах и различных формах акушерской патологии. Имеются обзоры и клинические исследования, показавшие отсутствие отрицательного влияния умеренной гемодилюции со снижением концентрации гемоглобина на течение и исходы беременности, а в ряде работ демонстрируется снижение частоты мертворождения и преэклампсии на фоне наличия легкой анемии[4,5]. Высокий уровень гемоглобина во время беременности, напротив, рассматривается как потенциальный предиктор преэклампсии: по некоторым данным, – выше 119 г/л в третьем триместре [2]. Однако данная альтернативная точка зрения на роль анемии при беременности в настоящее время не получила широкого распространения и обсуждения в акушерстве.

Мы предположили, что в группе женщин, имеющих факторы тромботического риска, предрасполагающие к возникновению протромботического состояния гемостаза, ожидаемое положительное влияние гемодилюционной анемии легкой степени на перинатальные исходы может быть более выраженным, чем в группе здоровых женщин без отягощенного анамнеза.

Цель: изучить влияние на течение и исход беременности анемии различной степени тяжести и

Author: Nova Clinic, Reproductive and genetic centre, Moscow, Russia.
e-mail: lидуhe@inbox.ru

этиологии (железодефицитная и гемодилуционная) в зависимости от наличия у пациенток факторов тромботического риска.

Методы. Проведено исследование по типу «случай-контроль» - ретроспективный анализ историй беременности и родов 454 женщин, завершивших беременность в 2015 году и состоявших на диспансерном учете в женской консультации клиники ФГБОУ ВО ЮУГМУ. Способ включения – сплошной. Критерии включения: наличие подтвержденной беременности, наличие в медицинской карте хотя бы одного общего анализа крови, а при выявлении анемии – дополнительно наличие результата обследования на сывороточное железо. Критерии исключения: многоплодная беременность, поздняя первая явка в женскую консультацию (после 25 недель гестации), тяжелые соматические и психические заболевания в стадии декомпенсации (в частности, исключены пациентки с сахарным диабетом 1 типа), смена лечебного учреждения наблюдения во время беременности.

Оцениваемые показатели: концентрация гемоглобина в каждом из триместров, наличие или отсутствие гипохромии эритроцитов (среднее содержание гемоглобина в эритроците - MCH - менее 27 пг), микроцитоза (средний объем эритроцита – MCV – менее 80 фл), уровень сывороточного железа. Пациентки с гипохромией, микроцитозом и уровнем сывороточного железа 12,5 мкг/л и ниже, согласно критериям, были отнесены к железодефицитной анемии (ЖДА), тогда как нормоцитарная нормохромная анемия без снижения сывороточного железа считалась гемодилуционной.

Конечными точками были выбраны: невынашивание беременности (самопроизвольные аборты: ранние – до 12 недель, поздние – с 12 до 22 недель гестации, и антенатальная гибель плода после 22 недели); развитие преэклампсии; хроническая плацентарная недостаточность (задержка роста плода по данным ультразвуковой фетометрии, гемодинамические нарушения в системе «мать-плацента-плод»); преждевременные роды на сроке 23-36 недель гестации; рождение гипотрофичного плода (масса тела при рождении оценивалась с помощью сигмальных таблиц физического развития новорожденного Г.М. Дементьевой).

К группе пациенток, имеющих факторы тромботического риска (далее – группа риска), были отнесены следующие: возраст 35 лет и старше, индекс массы тела 25 кг/м² и выше, отягощенный акушерский анамнез (невынашивание беременности, бесплодие, неудачи ЭКО, аборты, плацента-опосредованные осложнения в анамнезе - преэклампсия, плацентарная недостаточность, отслойка хориона/плаценты), индуцированная настоящая беременность, курение на

любом сроке гестации, наличие варикозного расширения вен, отягощенный семейный анамнез (острые сосудистые события в возрасте до 55 лет либо необъяснимый синдром потери плода, преждевременные роды, преэклампсия у родственников 1-2 линии), наличие артериальной гипертензии (хронической и гестационной), аутоиммунной патологии (неспецифический язвенный колит, системные заболевания соединительной ткани, аутоиммунный тиреоидит, циркуляция антифосфолипидных антител), хронической герпес-вирусной инфекции. Пациентки без указанных факторов риска были отнесены к группе низкого риска. Согласно документации, все случаи анемии во время беременности (уровень гемоглобина ниже 111 г/л) подлежали лечению препаратами железа, преимущественно в двухвалентной форме.

Статистические расчеты произведены с помощью пакета программ SPSS 22.0. После предварительного проведения анализа таблиц сопряженности с расчетом отношения шансов с 95% доверительным интервалом использован метод пошаговой логистической регрессии. Статистически значимыми считались значения $p < 0,05$.

Результаты. В группе риска ($n=343$) у 192 пациенток (56%) хотя бы в одном из триместров беременности регистрировалась анемия, в том числе средней и тяжелой степени – у 15 человек (4,4%). В группе низкого риска ($n=111$) аналогичные показатели составили соответственно 71 (64%) и 10 (9%).

В группе риска пациентки с исходом «невынашивание» значимо реже имели в течение беременности анемию легкой степени хотя бы в одном из триместров в сравнении с женщинами, завершившими беременность родами живым плодом, – по данным регрессионного анализа, ОШ 0,127; 95%ДИ 0,036-0,449; $p=0,001$. В группе низкого риска не было обнаружено связи частоты невынашивания с наличием анемии.

В группе риска уровень гемоглобина выше 140 г/л в первом триместре независимо ассоциирован с развитием преэклампсии (ОШ 5,183; 95%ДИ 1,445-18,588; $p=0,012$, метод – множественная логистическая регрессия). В группе низкого риска указанная взаимосвязь не наблюдалась.

В группе риска установлена независимая ассоциация между наличием анемии средней либо тяжелой степени в первом триместре беременности и развитием плацентарной недостаточности (ОШ 13,707; 95%ДИ 1,477-127,221; $p=0,021$; метод – множественная логистическая регрессия). В группе низкого риска анемия не была связана с плацентарной недостаточностью.

Для объединенной группы ($n=454$) обнаружена независимая ассоциация наличия анемии

средней и тяжелой степени в 1 триместре с преждевременными родами (ОШ 8,230; 95%ДИ 1,500-45,140; $p=0,015$; метод – множественная логистическая регрессия).

Не установлено каких-либо взаимосвязей наличия анемии с развитием задержки роста плода и преэклампсии ни в группе риска, ни в группе низкого риска, ни в объединенной группе.

Для дальнейшего анализа из каждой группы были исключены медицинские карты, не содержащие данных о среднем объеме эритроцита, среднем содержании гемоглобина в эритроците и уровне сывороточного железа, после чего группа риска составила 298 человек, а группа низкого риска – 100 человек. Дальнейший анализ проводился для данных групп.

В группе риска частота гемодилуционной анемии составила 38,6% (116 случаев), в том числе средней и тяжелой степени – 2,7% (8 случаев) от общего числа наблюдений. В группе низкого риска аналогичные показатели составили соответственно 42% (42) и 5% (5). ЖДА встречалась в 7% случаев (21 человек) в группе риска и в 5% (5 случаев) в группе низкого риска.

Ассоциированной с невынашиванием оказалась только гемодилуционная анемия в группе риска (ОШ 0,231; 95%ДИ 0,051-1,045; $p=0,054$). В группе низкого риска связи анемии и невынашивания не выявлено. Железодефицитная анемия не оказывала влияния на частоту живорождений.

В группе низкого риска инфекции мочевыводящих путей во время беременности значимо чаще наблюдались у пациенток, имевших гемодилуционную анемию (ОШ 2,802; 95%ДИ 1,038-4,323; $p=0,038$). Для группы риска, а также для железодефицитной анемии в обеих группах связь наличия анемии и инфекций мочевыводящих путей не наблюдалась.

Выводы. Подавляющее большинство случаев анемии в исследуемой группе беременных женщин относились к гемодилуционной, в то время как ЖДА встречалась лишь у 5-7% пациенток.

Наши данные предположительно указывают на положительное влияние гемодилуционной анемии легкой степени на исход беременности у женщин, имеющих факторы тромботического и акушерского риска: данный тип анемии значимо реже встречался у пациенток с невынашиванием. Вероятный механизм благоприятного влияния, возможно, связан с компенсаторным эффектом гемодилуции в отношении протромботического состояния гемостаза на фоне имеющихся факторов тромботического риска.

Высокий исходный уровень гемоглобина у женщин группы риска, вероятно, усугубляет протромботическое состояние за счет

гемооконцентрации, что может приводить к нарушению формирования плаценты на ранних сроках гестации и последующему развитию преэклампсии.

Для женщин без факторов риска и отягощенного анамнеза высокий исходный уровень гемоглобина не влияет на прогноз преэклампсии, а наличие гемодилуционной анемии не улучшает исходы беременности.

Наличие анемии любого типа средней или тяжелой степени с первого триместра беременности является неблагоприятным фактором в отношении возникновения плацентарной недостаточности (для женщин из группы риска) и преждевременных родов (для объединенной группы в целом).

Более высокая частота инфекций мочевыводящих путей у женщин без факторов риска с гемодилуционной анемией, возможно, связана с приемом препаратов железа без соответствующих показаний (отсутствие подтвержденного дефицита железа). Наличие ЖДА не оказывало влияния на частоту инфекций, вероятно, в связи с тем, что назначаемые препараты железа восполняли истинный дефицит железа, что существенно снижало побочные эффекты.

Таким образом, на наш взгляд, при решении вопроса о целесообразности медикаментозного лечения анемии во время беременности следует не только определять этиологию и степень тяжести анемии, но и сопоставлять эти данные с имеющимися факторами тромботического риска и акушерским анамнезом.

Наше исследование имеет ряд ограничений; в частности, не были учтены другие показатели, характеризующие обмен железа (ферритин, общая железосвязывающая способность сыворотки) по причине отсутствия результатов соответствующих исследований в медицинской документации. Требуется дальнейшее изучение вопроса для уточнения конкретных значений уровней гемоглобина, ассоциированных с неблагоприятными исходами беременности, а также углубленное изучение показателей обмена железа при беременности в зависимости от наличия факторов риска.

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Maternal and Perinatal Outcome in Patients with HELLP Syndrome

By Rohit Chandrakant Kamble & Nilima. S. Gupte

Abstract- HELLP syndrome (haemolysis, elevated liver enzymes, and low platelets) is a component of hypertensive disorders of pregnancy which is associated with significant maternal as well as perinatal morbidity and mortality. Maternal mortality is due to consequences such as pulmonary oedema, renal failure, disseminated intravascular coagulation and subcapsular liver hematoma. Perinatal mortality appears to be primarily related to the gestational age at the time of delivery. This study evaluates the maternal and perinatal outcome in HELLP syndrome so that the management is improved resulting in reduced mortality and morbidity.

Objectives: A. To study maternal outcome in patients diagnosed with HELLP syndrome. B. To study perinatal outcome in patients with HELLP syndrome.

Keywords: HELLP syndrome, maternal and perinatal outcome.

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Maternal and Perinatal Outcome in Patients with HELLP Syndrome

Rohit Chandrakant Kamble ^α & Nilima. S. Gupte ^σ

Abstract- HELLP syndrome (haemolysis, elevated liver enzymes, and low platelets) is a component of hypertensive disorders of pregnancy which is associated with significant maternal as well as perinatal morbidity and mortality. Maternal mortality is due to consequences such as pulmonary oedema, renal failure, disseminated intravascular coagulation and subcapsular liver hematoma. Perinatal mortality appears to be primarily related to the gestational age at the time of delivery. This study evaluates the maternal and perinatal outcome in HELLP syndrome so that the management is improved resulting in reduced mortality and morbidity.

Objectives: A. To study maternal outcome in patients diagnosed with HELLP syndrome. B. To study perinatal outcome in patients with HELLP syndrome.

Methods: This study was conducted in department of obstetrics and gynaecology of medical college and tertiary health care centre. A consecutive series of 56 pregnant women above 24 weeks of gestational age with HELLP syndrome were admitted at a tertiary care hospital, during the period of 24 months from 30th November, 2015 to 31st October, 2017. History, clinical data, detailed laboratory investigations were studied and categorized by Mississippi classification for better analysis of complication and outcome in HELLP syndrome.

Results: Total 56 cases of HELLP syndrome were studied. Majority of the patients were primigravidae belonging to lower socio-economic status, which were unbooked with no proper antenatal care. 60.71% of the patients had maternal complications. The complications were severe anemia in 21.43%, renal complication in 21.43%, DIC in 19.64%, abruption 14.29%, respiratory complication 7.15%, ascites 3.57% and septicemia in 3.57% and maternal mortality rate was 14.28%. A high incidence of perinatal morbidity and mortality (46.43%) was seen. Major contributing factors being prematurity, fetal growth restriction and birth asphyxia.

Conclusion: HELLP syndrome is associated with increased maternal and perinatal morbidity and mortality. Once diagnosis is made, it warrants aggressive intervention with control of blood pressure, antiepileptic prophylaxis and corticosteroid treatment and delivery. We have to increase grass root level antenatal care. Early detection and prompt management of pre-eclampsia is the most important approach to the prevention of HELLP syndrome.

Keywords: HELLP syndrome, maternal and perinatal outcome.

Author α: PG Resident, Department of Obstetrics and Gynaecology, Dr. Vasntrao Pawar Medical College, Hospital and Research Centre, Nashik – 422003, Maharashtra, India. e-mail: imrk16@gmail.com,

Author σ: Professor, Department of Obstetrics and Gynaecology, Dr. Vasntrao Pawar Medical College, Hospital and Research Centre, Nashik – 422003, Maharashtra, India. e-mail: guptenilima@yahoo.com

I. INTRODUCTION

Every woman wishes to have a healthy pregnancy which culminates in a healthy baby and a healthy mother. Unfortunately, some women develop dreaded complications that may result in adverse obstetric outcomes. These include Hypertensive disorders of pregnancy, Pre-eclampsia, Eclampsia and HELLP syndrome¹. Pre-eclampsia occurs in 5-10% of pregnancies². The HELLP syndrome (haemolysis, elevated liver enzymes, and low platelets) is a variant of severe pre-eclampsia that is associated with significant maternal and perinatal morbidity and mortality³. HELLP syndrome develops in 6-12% of women with preeclampsia or eclampsia accounting for 0.4-0.7% of all pregnancies⁴. Maternal mortality is due to consequences such as pulmonary oedema, renal failure, disseminated intravascular coagulation and subcapsular liver hematoma⁵. Perinatal mortality appears to be primarily related to the Maternal and Perinatal Outcome in Patients with HELLP Syndrome gestational age at the time of delivery⁶. HELLP syndrome is regarded as high risk for the mother and neonate compared to pre-eclampsia. Early diagnosis and identification of complication of HELLP syndrome and timely intervention form the main strategy of management.⁷

II. AIMS AND OBJECTIVES OF THE STUDY

- To study maternal outcome in patients diagnosed with HELLP syndrome
- To study perinatal outcome in these patients with HELLP syndrome.

III. METHODOLOGY

This was prospective observational study done over a period of 24 months i.e., Nov. 2015 to Oct. 2017. Total 56 cases of HELLP syndrome were studied. This study was conducted in department of obstetrics and gynaecology of medical college and tertiary health care centre

a) Inclusion Criteria

- All antenatal patients with pre-eclampsia and eclampsia complicated with HELLP syndrome.

b) Exclusion Criteria

- All patients with chronic hypertension

- Patients with any systemic illness
- Patients with hematological disorders
- Patients with renal and liver disorders
- Patients with autoimmune disorders

56 patients who were diagnosed as HELLP syndrome complicating preeclampsia and eclampsia were included in the study after satisfying inclusion and exclusion criteria. Written informed consent was taken from patients. After admitting the patients detailed history, complete general examination, systemic and obstetric examinations was done. Laboratory investigations for confirmation of HELLP syndrome and preeclampsia were done.

HELLP syndrome cases were classified according to mississippi classification

c) *Mississippi Classification (University of Mississippi 2006 Criteria)*

| | |
|-----------|---|
| Class I | Platelet < 50,000/mL AST or ALT > 70 IU/L LDH > 600 IU/L |
| Class II | Platelet 50,000-1,00,000/mL AST or ALT > 70 IU/L LDH > 600 IU/L |
| Class III | Platelet 1,00,000-1,50,000/mL AST or ALT > 40 IU/L LDH > 600 IU/L |

IV. RESULTS

The following data was obtained from the present series of 56 cases studied at tertiary care hospital, in department of obstetrics and gynaecology from 30th November, 2015 to 31st October, 2017.

Table 1: A classification of HELLP as per Mississippi's classification Class

| Class | No of Patients | Percentage |
|---------|----------------|------------|
| Class 1 | 10 | 17.86% |
| Class 2 | 23 | 41.07% |
| Class 3 | 23 | 41.07% |
| Total | 56 | 100.00% |

Majority of the cases belonged to class II and class III HELLP, 23 each (41.07%) followed by class I HELLP, 10 (17.86%).

Table 2: No. of cases according to age group

| Age Group in years | Class 1 | Class 2 | Class 3 | Total | % |
|--------------------|---------|---------|---------|-------|---------|
| < 20 | 2 | 3 | 5 | 10 | 17.86% |
| 20-24 | 4 | 13 | 10 | 27 | 48.21% |
| 25-29 | 1 | 7 | 6 | 14 | 25.00% |
| 30-34 | 2 | 0 | 2 | 4 | 7.14% |
| >35 | 1 | 0 | 0 | 1 | 1.79% |
| Grand Total | 10 | 23 | 23 | 56 | 100.00% |

48.21% of cases were in the age group 20-24 years (Table 2).

Table 3: No. of cases according to parity

| Gravida/Para | Class 1 | Class 2 | Class 3 | Total | % |
|--------------|---------|---------|---------|-------|---------|
| Primi | 5 | 12 | 16 | 33 | 58.93% |
| Multi | 5 | 11 | 7 | 23 | 41.07% |
| Total | 10 | 23 | 23 | 56 | 100.00% |

In present study 58.93% were primigravidae, while 41.07% of patients were multiparous (Table 3). In our study 24 (42.85%) cases of HELLP syndrome were seen of more than 37 weeks of gestation. (Table 4).

Table 4: No. of cases according to gestational age

| | Class 1 | Class 2 | Class 3 | Total | % |
|--------------|---------|---------|---------|-------|-------|
| < 28 weeks | 3 | 1 | 5 | 9 | 16.07 |
| 29- 32 weeks | 1 | 5 | 2 | 8 | 14.28 |
| 33- 36 weeks | 3 | 7 | 5 | 15 | 26.78 |
| > 37 weeks | 3 | 10 | 11 | 24 | 42.85 |

Table 5: Distribution of cases according to severity of hypertension

| Clinical signs | Class 1 | Class 2 | Class 3 | Total | % |
|----------------|---------|---------|---------|-------|--------|
| BP | Mild | 2 | 8 | 10 | 35.71% |
| | Severe | 8 | 15 | 23 | 64.29 |

In present study majority of the patients presented with severe preeclampsia and there were 20 cases (35.71%) with mild pre-eclampsia.

Maximum patients i.e., 58.92% of HELLP syndrome had platelet count less than 1lakh/ml. Serum lactate dehydrogenase was raised in all patients with HELLP syndrome. All patients with HELLP syndrome had raised serum AST was 70IU/L.55.36% (31 cases) had bilirubin levels > 1.2 mg/dl while 44.64% (25 cases) had bilirubin levels < 1.2 mg/dl.25% (14 cases) had abnormal renal function parameters.67.86% (38 cases) had serum uric acid levels > 6 mg/dl 33 cases (58.93%) required transfusion of blood or components while 23 cases (41.07%) did not require any blood and blood products.

Table 6: No. of cases according to laboratory investigations

| | Class 1 | Class 2 | Class 3 |
|------------------|---------|---------|---------|
| platelet | 10 | 23 | 23 |
| LDH >600 IU/L | 25 | 20 | 11 |
| AST/>70 IU/L | 30 | 16 | 10 |
| UA>6mg | 8 | 15 | 15 |
| Bilirubin >1.2 | 8 | 14 | 9 |
| Srcreat>1.2mg/dl | 5 | 4 | 5 |

Table 7: Distribution of cases according to blood and blood products

| Blood and blood products Transfusion | Class 1 | Class 2 | Class 3 | Grand Total | % |
|--------------------------------------|---------|---------|---------|-------------|---------|
| Not Transfused | 0 | 8 | 15 | 23 | 41.07% |
| Transfused | 10 | 15 | 8 | 33 | 58.93% |
| Grand Total | 10 | 23 | 23 | 56 | 100.00% |

Table 8: Cases according to maternal outcome

| | Class 1 | Class 2 | Class 3 | Total | % |
|----------------|---------|---------|---------|-------|-------|
| Anemia | 4 | 5 | 3 | 12 | 21.43 |
| Pum edema | 1 | 1 | 0 | 2 | 3.57 |
| Resp infection | 1 | 1 | 0 | 2 | 3.57 |
| Oliguria | 1 | 1 | 0 | 2 | 3.57 |
| Hematuria | 1 | 1 | 1 | 3 | 5.36 |
| Renal failure | 4 | 3 | 0 | 7 | 12.50 |
| Abruption | 4 | 3 | 1 | 8 | 14.29 |
| DIC | 8 | 3 | 0 | 11 | 19.64 |
| Ascites | 0 | 1 | 1 | 2 | 3.57 |
| sepsis | 1 | 1 | 0 | 2 | 3.57 |
| Death | 2 | 4 | 2 | 8 | 14.28 |

Table 9a: Perinatal outcome

| | Class 1 | Class 2 | Class 3 | Grand Total | % |
|----------------|---------|---------|---------|-------------|--------|
| Pre Term | 11 | 10 | 5 | 26 | 46.43% |
| APGAR <6 | 16 | 12 | 7 | 35 | 62.50% |
| IUGR | 9 | 7 | 1 | 17 | 30.36% |
| MAS | 3 | 2 | 2 | 7 | 12.50% |
| Sept | 0 | 1 | 0 | 1 | 1.79% |
| NICU admission | 11 | 10 | 4 | 25 | 44.64% |

Table 9b: Perinatal outcome

| | Class 1 | Class 2 | Class 3 | Total | % |
|-------------|---------|---------|---------|-------|-------|
| Live birth | 6 | 17 | 13 | 36 | 64.29 |
| Still birth | 3 | 5 | 6 | 14 | 25.00 |
| IUFD | 1 | 1 | 4 | 6 | 10.71 |
| END | 1 | 3 | 2 | 6 | 10.71 |
| Take home | 5 | 14 | 11 | 30 | 53.57 |

V. DISCUSSION

HELLP syndrome is life threatening complication considered to be variant of preeclampsia and eclampsia. Early identification of risk factors in pregnancy and timely intervention gives better maternal and perinatal outcome.

In our study mean maternal age was 23.09 ± 4.45 (18-35 years) which was comparable to James N Martin *et al.*,⁸ (1991) 22.9 ± 5.5 (14-42 years).

Majority of the patients in the present study were primigravidas (33 cases) 58.93% comparable to Sibai BM Taslim *et al.*,² (1986) 52% and Martin JN *et al.*,⁹ (1999) 51%.

Systolic BP in this study was class I 138 ± 4 , class II 151 ± 18 and class III 175 ± 12 which were comparable to Martin JN *et al.*,⁸ class I 156 ± 24 , class II 158 ± 22 and class III 163 ± 19 .

Majority of the patients in this study delivered vaginally 83.93% which was higher than Vigil P de Gracia⁷ 29% and Shafika Banoo¹⁵ 60%.

Table 10: Maternal outcome

| Complications | Imir GA ¹⁰ | Vigil P de 7 Gracia ⁷ | Fernandez ¹¹ | Haddad et al ¹² | Ahmed et al ¹³ | Present study |
|-------------------|-----------------------|----------------------------------|-------------------------|----------------------------|---------------------------|---------------|
| DIC | 17% | - | 38% | 8% | 62.5% | 19.64% |
| Respiratory | 25% | - | 1.1% | 10% | - | 7.15% |
| ARF | 25% | 12% | 4% | 5% | 18.75% | 12.5% |
| Ascites | 14% | - | - | 5% | - | 3.57% |
| Abruptio placenta | 10.9% | 12% | 28% | 10% | 25% | 14.29% |
| Hematuria | 4.6% | 22% | - | - | - | 5.36% |
| Sepsis | 3.1% | - | - | - | - | 3.57% |

Majority of the HELLP were full term i.e., gestational age >37 weeks (42.85%) comparable to Vigil P de Gracia⁷ 40%.

Table 11: Perinatal outcome

| Complications | Kim YH ⁶ | Sibai BM et al ² | Svendson HK ¹⁴ | Imir GA ¹⁰ | Present study |
|----------------|---------------------|-----------------------------|---------------------------|-----------------------|---------------|
| NICU admission | 85.7% | 28.3% | - | - | 44.64% |
| Preterm | - | - | 70% | - | 46.43% |
| IUGR | 47.6% | 31.6% | 38.6% | 54.7% | 30.36% |
| Still birth | - | 19.5% | - | - | 25% |
| IUD | 4.8% | - | - | 18.8% | 10.71% |
| APGAR <6 | 66.7% | 28.5% | - | 37.5% | 62.5% |
| RDS | 38.1% | - | 40% | 23.4% | - |
| Sepsis | 85.7% | - | - | 7.8% | 1.79% |
| Neonatal death | 19.5% | 17.4% | - | 20.3% | 10.71% |

Cesarean delivery in present study was 16.07% which was lesser than Vigil P de Gracia⁷ 71% and Shafika Banoo¹⁵ 40% and Haddad et al.,¹² 63%. Majority of the indication for cesarean section were fetal distress, CPD, previous cesarean section and worsening maternal parameters with failed induction.

In this present study transfusion of blood and blood products was required in 58.93% which was comparable with Imir GA¹⁰ 62.5% and higher than Vigil P de Gracia⁷ 29%.

In the present study, DIC 19.64% was lesser than Ahmed et al.,¹³ 62.5%, Fernandez¹¹ 38.1%, but higher than Haddad et al.,¹² 8%. Abruptio in the present study 14.29% was comparable to Haddad et al.,¹² 10%, Imir GA¹⁰ 10.9%, Vigil P de Gracia⁷ 12%, but lesser than Ahmed et al.,¹³ 25% and Fernandez¹¹ 28%. This is because of early recognition and prompt treatment of severe preeclampsia with HELLP. Acute renal failure in the present study 12.5% was comparable to Haddad et al.,¹² 5%, Fernandez¹¹ 4%, but lesser than Imir GA¹⁰ 25%.

Ahmed *et al.*, 13.75% and Vigil P de Gracia⁷ 12%. Ascites in the present study was 3.57% comparable to Haddad *et al.*,¹² 5%, but lesser than Imir GA¹⁰ 14%. Sepsis in the present study was 3.57% comparable to Imir GA¹⁰ of 3.1%.

In this present study, maternal mortality was 14.28% and was higher than Imir GA¹⁰ 7.8% and Ahmed *et al.*,¹³ 6.25%. It is higher than Haddad *et al.*,¹² 1%, Vigil P de Gracia⁷ 2.3%, Haram K *et al.*,¹⁴ 2.5% and Sibai BM 1.8%.

In this present study, preterm babies were 26 i.e 46.43% was lesser than Svendsen H¹⁴ 70%.

For APGAR <6, 62.5% in this study was comparable to Kim YH⁶ 66.7%, IUGR 30.36% comparable to Sibai *et al.*,² 31.6%, still birth 25% comparable to Sibai *et al.*,² 19.5%. Neonatal death in this study 10.71% was comparable to Sibai *et al.*,² 17.4%. IUD 10.71% in this study was lesser than Imir GA¹⁰ 18.8% and higher than Kim YH⁶ 4.8%.

In this present study, perinatal mortality (46.43%) was comparable to Gul *et al.*,¹⁶ 42%, but higher than Sibai BM 33.3%, Magann EF *et al.*,¹⁷ 23.2% and Willey Visser¹⁸ 14.1%. Majority of the causes of Perinatal mortality in our study were prematurity (46.43%), still birth (25%), SGA (30.36%) and birth asphyxia (83.33%).

VI. CONCLUSION

In our study done over a period of 2 years, there were 56 cases of HELLP syndrome. Once the diagnosis of HELLP syndrome has been made, it warrants aggressive intervention with control of blood pressure, antiepileptophyl axis, corticosteroid treatment for fetal lung maturity and expeditious delivery. HELLP syndrome, among pre-eclampsia and eclampsia cases is associated with significant maternal morbidity and mortality and perinatal mortality and morbidity. The present study shows maternal mortality of 14.28% but still perinatal mortality constitutes 46.43%. In order to reduce the maternal and perinatal mortality, It is highly desirable that obstetric care providers at all levels become knowledge able about the early diagnosis and management of HELLP syndrome.

We have to intensify our efforts to reduce preeclampsia with HELLP syndrome from the grass root level with regular antenatal care, early detection of pre-eclampsia and its prompt management and early detection of complications with timely intervention. This will go a long way in preventing this catastrophic disease.

Vigilant fetal monitoring (including electronic fetal monitoring), prompt timely intervention at the periphery and improvement of neonatal care facilities with good prenatal care at the foremost are needed to reduce the perinatal mortality in the present study.

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

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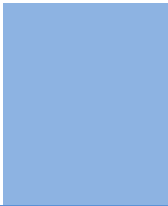
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Acknowledgments

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

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

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



Manuscript Style Instruction (Optional)

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

Structure and Format of Manuscript

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

A research paper must include:

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

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

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

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

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



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

All manuscripts submitted to Global Journals should include:

Title

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

Author details

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

Abstract

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

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

Keywords

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

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

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

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

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

Numerical Methods

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

Abbreviations

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

Formulas and equations

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

Tables, Figures, and Figure Legends

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



Figures

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

PREPARATION OF ELETRONIC FIGURES FOR PUBLICATION

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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



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

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

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

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

INFORMAL GUIDELINES OF RESEARCH PAPER WRITING

Key points to remember:

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

Final points:

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

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The discussion section:

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

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

General style:

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

Title page:

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

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

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

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

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

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

Approach:

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

Introduction:

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



The following approach can create a valuable beginning:

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

Approach:

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

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

Procedures (methods and materials):

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

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

Materials:

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

Methods:

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

Approach:

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

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

What to keep away from:

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



Results:

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

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

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

Content:

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

What to stay away from:

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

Approach:

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

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

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

Figures and tables:

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

Discussion:

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

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

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



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

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

Approach:

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

Describe generally acknowledged facts and main beliefs in present tense.

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| <i>References</i> | Complete and correct format, well organized | Beside the point, Incomplete | Wrong format and structuring |



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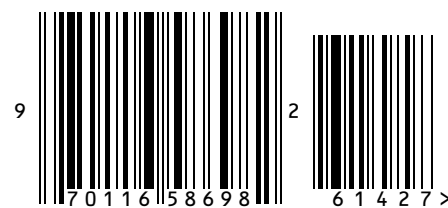
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