IJOPARB appears in the recommended list of Journals of University Grant Commission: Sl.No: 180; Jr.No. 62671; ISSN: 22499784

ISSN 2249 -9784
Volume 07, No. 02
April-June 2017

IJOPARB

Indian Journal of Perinatology and Reproductive Biology

Official Journal of Indian Society of Perinatology and Reproductive Biology

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Vol. 07 | No. 02 | April-June 2017 | ISSN 2249-9784

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Official Journal of
INDIAN SOCIETY OF PERINATOLOGY AND
REPRODUCTIVE BIOLOGY (ISOPARB)

Indian Society of Perinatology and Reproductive Biology

Estd. 1978

(Reg No. 71 of 1978-1979 under the Societies Registration Act 21 of 1860)

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ISSN 2249-9784 **RNI No. WB ENG/2010/39056**

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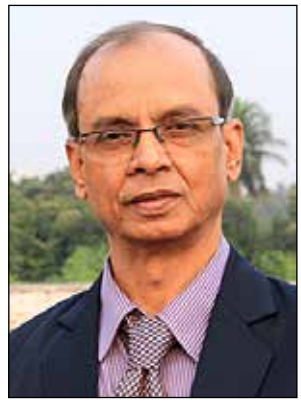
Editor's Choice

Indian Journal of Perinatology and Reproductive Biology (IJOPARB)



"If the winter comes, can spring be far behind?"

—PB Shelley

It's time to say goodbye to Northwind and welcome the Southwind. Winter bids adieu and spring announces its arrival. Spring steps in with its colours, song and dance. We welcome the long awaited great festival of India "Holi hai !"

Good part on behalf of the editorial board of the IJOPARB and the members of ISOPARB, is more and more feedbacks from readers and members. Interests are shown by the members to submit articles, updating addresses and requests for new membership of the society. Most important, is the appreciation of the journal (IJOPARB) by members. We express our sincere thanks to all for the appreciation.

Indian Journal of Perinatology and Reproductive Biology (IJOPARB) is an editorially independent journal of *Indian Society of Perinatology and Reproductive Biology* (ISOPARB). IJOPARB aims to provide the health professionals working in obstetrics, gynecology and allied disciplines of medicines, perinatology, reproductive biology and others, with uptodate knowledge and peer reviewed articles. Our target readers, are the specialists, trainee residents, post graduates of the related disciplines.

Further good news are the requests from the trainee residents for more CMEs, revision courses and workshops from the society. The Delhi Chapter of ISOPARB has already led the path by organizing courses at Sir Gangaram Hospital. Probably ISOPARB and its state branches can organize more such courses in different zones of the country to meet the demand.

Besides the academic activities members of ISOPARB are involved in improving women's and perinatal health. Dr Milind Shah, the President of ISOPARB, is to introduce a project to improve the safety of surgery and anesthesia with the use of a high quality pulse oximeter. The project is supported by 'Life Box Foundation', a charitable organization based in UK and USA. We all know, the use of pulse oximeter and WHO safety checklist have reduced surgical morbidity and mortality by more than 30%. We welcome the project by the President of ISOPARB.

By the time this issue of IJOPARB is released and reaches the members, we all are there in Mumbai for the annual conference of the society. We have received the communication from the society about the conference (See back cover). We are to participate the conference for the social, cultural and academic exchange.

The editorial board members are very pleased to release this issue of IJOPARB with its high quality contents. I am sure you all will enjoy this issue.

The article, '*Packing in Obstetrics*' by the Editor-in-Chief, has got its views and counterviews. It is related to management of emergencies in manipulative and operative obstetrics. We need to know the alternatives of management in obstetric hemorrhage. One need to decide the most appropriate management for an individual patient depending on the resources available.

The article '*Hapatitis E in Pregnancy*' by Dr Divya Arora and Prof Ashok Kumar, and the other, 'Post partum collapse' by Dr Md. Aftabuddin Mondal, Dr

Anuradha De and Prof Shyamapada Pati are the must read.

In Hepatitis E, genome variations, viral replication, high steroid levels, the severity of infection and the maternal and perinatal outcome have been well explained.

The article, *Post partum Collapse* is due to the *Critical illness related corticosteroid insufficiency* (CIRCI). CIRCI results in profound hypotension which is refractory to fluid replacement therapy. We all should share the authors' experience. Umbilical cord coiling index, by Dr Babita Saha and Prof Sajal Datta is another article of real clinical interest when we correlate it with perinatal outcome.

The case report on, *Infertility in relation to genital tuberculosis* reminds us about its importance over the years despite our increased awareness of this communicable disease. We need to be alert to consider this issue while managing a problem of subfertility, even these days.

The other case report, *Evans' Syndrome — successful pregnancy'*, is of much clinical and academic interest, fortunately rare though. We appreciate all the teachers and the associated authors for their contribution in the issue of IJOPARB and like to thank them all sincerely.

We request our members and readers to send their request for any particular topic of interest that we may consider in subsequent issue. We do expect feedback from our readers in the section '***Letters to the Editor***' for any query and comment.

Prof (Dr) Hiralal Konar
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Views & Counter Views

Packing in Current Obstetric Practice – A Forgotten Art

Professor (Dr) Hiralal Konar

Surgical packing in current obstetric practice is seen as a forgotten art like few other obstetric procedures. Uncontrolled bleeding in and around the genital tract at times becomes really troublesome and life threatening. Hemostatic sutures or the conventional measures may not be effective in some cases. Obstetric hemorrhage is the cause of maternal deaths both in the developing and the developed world. In obstetrics, besides the medical management, currently many new surgical interventions are being made to control massive obstetric hemorrhage. To mention, intrauterine balloon tamponade,[1] compression sutures, uterine devascularization procedures, hypogastric artery ligation, direct tissue suturing and many others are used to control obstetric hemorrhage. Introduction of fibrin sealants is an addition to clinician's armamentarium. Surgical haemostatic measures are so many. To name a few are, B-Lynch suture,[2] Cho square haemostatic suture, multiple U – suture (Hackethal), Hayman suture, and the Dawlatly suture. It is uncertain which method is the optimum for one case. There is no such controlled study to suggest which method is to be used with priority. Moreover, there is no such recommendation how long we should wait for one method before we declare it a failure and to proceed to the next.

It is not uncommon to face difficulties of hemostasis due to generalized oozing from a wide surface area of the pelvis. More worse condition is to face the extreme vaginal laceration, cervico-vaginal lacerations, vulval, paravaginal or broad ligament hematoma formation. These scenarios may be encountered following spontaneous vaginal delivery or following instrumental vaginal delivery.

It is more often than not in obstetrics, to see such situations to be complicated with disseminated intra vascular coagulation (DIC) and to make it more worse. In many such conditions, suturing is not only ineffective but may be counter-productive as it causes more tissue trauma and hemorrhage.

Tight intrauterine plugging even in early pregnancy complications has been done. Bleeding from injured uterine sinuses following evacuation is controlled successfully. Tight cervico-vaginal plugging is an invaluable measure to secure hemostasis in a case with cervical pregnancy. Golden moments are saved with this procedure when the evacuation procedure has been attempted inadvertently with the erroneous diagnosis of cervical abortion, for a case with cervical pregnancy. Often such a case ends fatally with the maternal death. Tight intracervical packing may again be a temporary measure while some more definitive surgery could be done depending upon the need of the patient. But this initial measure of tight cervical packing can save a woman.

In late pregnancy, bleeding from the uterine lower segment in placenta previa may be encountered following cesarean section. Suturing the uterine incision over a tight intrauterine pack, often controls the bleeding. Based on this principle isthmic – cervical suturing is made. To arrest re-inversion of uterus, it is useful to do intrauterine packing immediately following repositioning of the uterus while oxytocics are continued.

Intrauterine plugging with dry long roller gauze to combat post partum hemorrhage (PPH) have been attempted to preserve the uterus, when oxytocics and

bimanual compression have failed. More aggressive surgical measures to achieve complete primary hemostasis in such a patient, who is hemodynamically unstable, may be a futile attempt to save her.

Plugging may be the only option left, to control the hemorrhage even in an ideal or poor resource setting. Many obstetricians feel plugging has got its definite place either as a temporary or a permanent measure, even in present day obstetric practice to prevent maternal deaths due to massive obstetric hemorrhage.[3] When used as temporary measure it allows time to resuscitate the patient with volume replacement, blood or blood component therapy, use of vasopressure drugs for the next step of major surgery (hypogastric artery ligation or hysterectomy).

This maneuver of intrauterine plugging is facing controversy in current obstetric practice. Antagonists argue, it is unphysiological as we need to empty the uterus and not to fill it. Empty uterus initiates contractions. Protagonists argue, uterine packing raises the intrauterine pressure above the intravascular pressure. Moreover, packing stimulates myometrial contractions. Combined the mechanisms together hemostasis is achieved. Many obstetricians believe that the mechanism of intrauterine balloon tamponade is based on the concept of tight intrauterine plugging. The art of packing is important. The obstetrician plugging the uterus should remember, that it should be tight (often it is said "air tight"), uniform and cover the whole uterine cavity. Moreover, there should be no dead space left behind. An experienced obstetrician tackles the hemorrhage with proper packing more confidently rather than a hesitant person with little or no experience.

The underline principle of packing in obstetrics is that the tamponade pressure should rise above the arterial pressure. This raised pressure will control bleeding from the smaller arteries and the low pressure capillaries and the venous plexuses.[4] However tamponade pressure is unable to control bleeding from larger arteries. This means when the bleeding is from larger arteries, it needs to be controlled with surgical sutures, hypogastric artery ligation or arterial embolization.

Cases where DIC has set in or where hemorrhage is due to injury from the venous plexuses (paravesical or para urethral region) or from large raw surfaces, packing is an invaluable measure to achieve hemostasis. This is again important, specially when bleeding is from the inaccessible area (retropubic space). Author's personal experience and view is that we, the obstetricians, should practice the art of packing correctly and patiently. Packing is a mechanical method to exert tamponade (compression) effect to tissues to arrest bleeding.

Packing has been found to reduce mortality significantly in trauma patients.[5] In situations where the patient is hemodynamically unstable, packing allows time for resuscitation, correction of coagulopathy, use of vasopressor drugs, volume replacement and tranexamic acid. "Triad of Death" in trauma literature are: coagulopathy, acidosis (pH ≤ 7.2) and hypothermia (≤ 35°C).[6] Physiological changes in pregnancy are enormous and it affects all the systems of the body. Oxygen consumption in pregnancy is increased by 20%. Obstetric hemorrhage causes deterioration of body with homeostasis very rapidly. With uncontrolled obstetric hemorrhage, there is dramatic onset of hypovolemia, hypoxia , acidosis, DIC, and multi-organ dysfunction.

Pelvic compression **is helpful to control bleeding.** Pelvic tamponade with a Logethotopulas pack has been found to be useful in cases with bleeding following hysterectomy to control hemorrhage.[7] The principle is the same as discussed above. The method is also straight forward. A flexible plastic bag larger than the pelvic cavity is filled with dry gauze swabs. The neck of the bag is firmly tied and made tubular which is taken out of the pelvis through the vagina. It is then attached to a bottle of water and is allowed to hang freely over the end of the bed. This generates a steady and uniform tamponade as it moulds itself to compress the pelvic cavity uniformly. It stops bleeding from the smaller pelvic vessels and the venous plexuses except that of the major arterial bleeding. This maneuver has found to be life saving in cases where conventional methods have failed.[7]

Packing the pelvis through ***abdominal route*** has also been practiced to control hemorrhage following pelvic surgery.[8] It has also been found effective in cases with bleeding from pelvic venous plexuses where the uterus is well retracted. Large size (30 cm x 30 cm), X-ray detectable swabs are folded tightly in "sandwich sized" rolls. These are used to pack the pelvis around

the uterus to apply uniform and sufficient pressure against the bleeding sinuses. Within few minutes bleeding is expected to be controlled and the blood pressure is normalised. Abdomen is closed thereafter without closing the rectus sheath to avoid the risk of '*Compartmental Syndrome*'. Packs are removed after 24 hours with proper documentation.

A word of caution is proper selection of case is important. Packing should be done properly. Packing of the lower genital tract to control hemorrhage has got a definite place in obstetrics. Intrauterine packing has got its selected place as an alternative to hysterectomy. It may be a temporary measure in the bargain of time to go for more aggressive and definitive surgical procedures. Packing may be a temporary measure where resources for peripartum hysterectomy (surgical skill, theatre resources) are limited or absent and also where time is needed to transfer the patient to a higher centre. Packing is indicated in situations where obstetric hemorrhage is further complicated with DIC and where attempt of repeated suturing is counter-productive.

It is essential to keep in mind that all the packs should be removed after 24 hours with proper counting and documentation. The procedure "***pack and go back***" may prevent maternal morbidity and mortality, arising out of obstetric hemorrhage provided it is done in a select case, timely and properly.

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Review Article

"Hepatitis E" in Pregnancy

Dr Divya Arora,[1] Dr Ashok Kumar[2]

Introduction

Hepatitis E viral hepatitis (HEV) was first recognized in the Indian subcontinent in the 1950s, when the sera from persons during two water borne epidemics in India were negative for Hepatitis A and B.[1] HEV infection is transmitted mainly through faeco-oral route. Outbreaks of HEV are often reported in endemic countries, where most infections occur in young adults aged 15-45 years.[2]

HEV infection is a major public health problem in the developing countries. HEV infection in pregnancy is associated with adverse maternal and fetal outcomes such as high rates of spontaneous abortion, intrauterine death, preterm labor, low birth weight, maternal acute liver failure, disseminated intravascular coagulation, encephalopathy, need for intensive care, antepartum and post partum hemorrhage. HEV infection in pregnant women is more common and fatal in the third trimester. Although the mechanism of liver injury is not yet clear, it is possible that interplay of hormonal and immunologic changes during pregnancy, along with a high viral load of HEV, renders the woman more vulnerable. Immunologic changes during pregnancy promote the maintenance of the fetus in the maternal environment by suppression of T cell–mediated immunity, rendering pregnant women more susceptible to viral infections like HEV infection.

The outbreaks of Hepatitis E are large and the overall attack rates range from 1 to 15%, varying from 3–30% in adults to 0.2–10% in children. HEV infection can induce acute liver failure in pregnant women, leading to 20-30% mortality.[3] Fulminant hepatitis and hepatic encephalopathy are the main causes of death. Vertically transmitted HEV infection is known to cause acute hepatitis in newborn babies.[4] Fulminant liver failure was significantly higher in pregnant women with HEV infection as opposed to other causes of acute viral hepatitis (69.2% vs. 10%, $p<0.001$).[5]

Hepatitis E Virus

Hepatitis E virus (HEV), originally recognized as non-A and non-B hepatitis inducing agent, was recently classified into the genus Hepevirus and family Hepeviridae.[6] It is a single stranded non enveloped positive sense RNA virus, first described in 1983 as spherical, 27–30-nm virus-like particles. Its genome is approximately 7.3 kb in length. It also has a short 5' non-coding region (NCR), a 3' NCR and 3 open reading frames (ORFs). ORF1, ORF2 and ORF3 that encode nonstructural proteins including an RNA-dependent RNA polymerase, a capsid protein and a phosphorylated small protein respectively.[7]

Genotypes of Hepatitis E

The genomes of several HEV strains from different parts of the world have been sequenced and compared. They can be generally distinguished into four major

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✉ Dr Divya Arora

groups, namely genotype 1, 2, 3 and 4 respectively. These four major genotypes that may differ up to 20% at the nucleotide level,[8] but they are serologically indistinguishable and cross-reactive.

Genotype 1 includes isolates from Asia, the Middle East, and North Africa. Genotype 2 has been found in Mexico and Nigeria. Genotype 3 was recovered from swine in North America, Europe, Egypt, Asia and New Zealand and from humans in North and South America, Europe, Japan and China. Genotype 4 was found in humans and swine in Asia.

HEV genotypes are seen to correlate with the severity of infection.[9] Evidence suggests that genotype 1 is more pathogenic in humans than genotypes 3 and 4. In India, genotype 1 is the commonest genotype which explains the high severity of infection in comparison to US, where genotype 3 is the commonest genotype seen.

Epidemiology

Hepatitis E can occur either in large epidemics, or in the form of sporadic cases. HEV is transmitted via the faeco-oral route and is easily spread by water contaminated with human faecal matter. In the past, most of the hepatitis E outbreaks occurred after monsoon rains, heavy flooding, contamination of well water, or massive uptake of untreated sewage into city water treatment plants. Epidemics result from contamination of river water used for drinking, washing, bathing, and sewage disposal.[10] Open defecation in backyards and open fields can be another source of faecal contamination of groundwater, crops and waterways. Its transmission form person-to-person has also been reported.[11] Domestic pigs, wild boar, and sika deer are reservoirs for genotypes HEV-3 and HEV-4.[12] Human infections occur through three methods, namely, zoonotic foodborne consumption, direct contact with infected animals, and environmental contamination by animal manure run-off.[13] HEV has been occasionally linked to nosocomial spread.[14] Vertical transmission from mother to infant is also known to occur.[15] Rarely, it has been found to be transmitted by transfusion of blood or blood products.[16]

Developed countries that are non-endemic for HEV have sporadic cases of HEV which were associated with travel to endemic countries.[17,18] However, an increase number of acute HEV cases in people without any such travel history prompted a study of the overall HEV infection status and the origin of infections in several developed countries.[17] Serological studies indicated that a considerable proportion of people in developed countries had anti-HEV antibodies. For example, 19-21% of US blood donors had antibodies specific to HEV.[19] Studies conducted in several European countries such as England, Germany, Italy, and France demonstrated that the study populations also had relatively high rates (13-53%) of anti-HEV antibodies.[20,21] Similarly, seroprevalence studies in Asian countries such as Japan, South Korea, Hong Kong, Taiwan, and China have reported that approximately 6-43% of their populations had anti-HEV antibodies.[22] HEV in developed countries are now recognized as an emerging zoonotic disease.

The overall prevalence of seropositive HEV IgG was 33.67% among the pregnant women in a study conducted by Begum et al in 2009 in northern India.[23] The seropositivity of HEV IgG was significantly high in urban population ($p<0.05$), and was related with the period of settlement ($p<0.05$) and source of water ($p=0.05$). Low socio-economic status of the pregnant women appeared to be the only risk factor (OR=1.96, CI=1.17-3.28) associated with HEV IgG antibody positivity.

The secondary attack rate among exposed household members is low but significantly higher than the incidence of the disease unexposed control households (7.7 vs 1.3 per thousand population in the Rangoon outbreak).[24] This phenomenon is unusual for enterically transmitted agents and may be based on the relative instability of HEV virus.

Although, a high male to female ratio (approaching 3:1 in the Nepal epidemic)[25] has been reported, but other reports suggest a 1:1 ratio for clinical disease.

The highest attack rate among cases with clinically overt disease is observed between 15-30 years of age.[26] Hepatitis E infection is also frequently seen in children, most of them are asymptomatic and do not have signs of jaundice.

Clinical Presentation of Hepatitis E

Hepatitis E virus (HEV) usually causes an acute self-limited disease. The incubation period of varies from 2-9 weeks.

The clinical course is generally that of an acute hepatitis. It can progress to chronic hepatitis in transplant recipients or HIV infected individuals. Fulminant disease does occur in about 10% of cases. In women who are pregnant, HEV infection has a high case fatality rate of 15-20%.[23] Hepatitis E can present with a wide range of symptoms, from a subclinical case to chronic liver disease with extrahepatic manifestations. HEV can cause jaundice, vomiting, appetite loss, fatigue, hepatalgia and hepatomegaly. HEV-infected mothers can transmit the infection to fetus, leading to premature birth, increased fetal loss and hypoglycaemia, hypothermia, and anicteric or icteric acute hepatitis in the newborns. Occasional cases with atypical non-hepatic manifestations, such as acute pancreatitis, hematological abnormalities, autoimmune phenomena, and neurological syndromes have been reported from both hyperendemic and non-endemic regions. The pathogenesis of these manifestations remains unclear.

Virus Excretion and Viremia

HEV particles have been isolated from stools of patients and experimentally infected primates by immune electron microscopy.[27] Peak viraemia and peak shedding of HEV into the faeces occurs during the incubation period and early acute phase of the disease. The period of communicability is unknown but virus excretion in the stool has been demonstrated for up to 14 days after onset of jaundice and then disappears during the recovery phase.[28]

Bile specimens obtained before the liver enzyme activity elevation from infected rhesus monkeys were found to be more frequently positive for HEV RNA by RT PCR than were specimens obtained during the peak of transaminase levels.[29] In cynomolgus macaque infected with HEV, the presence of the viral genomic sequences in faeces and serum preceded the elevation of ALT levels.[30]

In other studies also,[31,32] it has been suggested that it may not be possible to detect the viral genome in the serum of all patients infected with HEV due to short period of viraemia which precedes the onset of clinical features of the disease.

Genomic Organisation of Hepatitis E Virus

The genome of mammalian HEV in the genus Hepevirus consists of a short 5' noncoding region (NCR), three open reading frames (ORFs 1, 2 and 3) and a 3' NCR.[33] ORF2 overlaps ORF3, but neither overlaps with ORF1.[34] A cap structure has been identified in the 5' end of the viral genome and may play a role in the initiation of HEV replication.[35]

The ORF1, located at the 5' end of the genome, encodes viral nonstructural polyproteins that are involved in viral replication. The ORF2, located at the 3' end of the genome, encodes the viral capsid protein that contains a typical signal peptide sequence and three potential glycosylation sites. It has been demonstrated that mutations within the glycosylation sites prevent the formation of infectious virus particles.[36] It has been shown that amino acid residues Leu477 and Leu613 in the capsid protein are important in forming the neutralization epitope.[37]

The ORF3 encodes a small cytoskeleton-associated phosphoprotein.[38] The N-terminus of ORF3 binds to HEV RNA and forms a complex with the capsid protein.[39] The C-terminus of the ORF3 protein is multifunctional and may be involved in virion morphogenesis and pathogenesis.[40] The ORF3 protein was shown to be responsible for virion egress or release from infected cells.

Hepatitis E in Pregnancy

HEV in pregnancy is a major public health problem in developing countries like India. Pregnancy appears to be a potential risk factor for viral replication due to altered immune system. HEV infection in pregnancy is more severe and often leads to severe maternal and fetal complications. One of the most distinctive features of the epidemic and endemic hepatitis E is higher occurrence and mortality of disease in pregnancy.[41] Thus, the disease incidence was 8 times higher and fulminant hepatic failure (FHF) occurred 13 times more often in pregnant women than age-matched men and non-pregnant women. Fulminant hepatic failure (FHF) during pregnancy has limited pre-encephalopathy interval, rapid progression, high occurrence of brain edema and coning of the cerebellar tonsils. However, frequent occurrence of disseminated intravascular coagulation (DIC) was distinct feature of this disease. Fulminant hepatic

failure was significantly higher in pregnant women with HEV infection as supposed to other causes of acute viral hepatitis (69.2% vs. 10%, p<0.001).[4] HEV in pregnant women causes substantial fetal and perinatal mortality. There are several studies reporting intrauterine transmission of HEV with high fetal and perinatal mortality.[42,43]

In a study carried out by Jaiswal et al, in Indore India in 2001,[44] 273 females with viral hepatitis were studied out of which 127 were pregnant. Among the 127 pregnant females, 83 were AVH cases out of which 57.5% had HEV infection, fifty eight percent of the HEV infected pregnant females were associated with FHF.

In a similar study conducted by Singh et al, in 2001,[45] 50 pregnant women with clinical hepatitis were included. 40% were positive with IgM anti HEV. The fatality rate in the second and third trimester was 66.6% and 71.43% respectively. Thus, it was concluded that HEV causes high mortality in pregnant women as compared to non-HEV pregnant women.

In a large prospective study from North India by Kumar et al in 2004 in Delhi,[46] it was found that 60% of viral hepatitis in pregnant women was attributed to hepatitis E infection. It was seen that approximately two-thirds of the pregnant women with HEV infection had preterm deliveries. The mortality rate among the HEV-positive pregnant women was 26.9%. Vertical transmission was observed in 33.3% of cases.

Fulminant Hepatic Failure

Fulminant hepatic failure (FHF) is a severe and usually fatal complication of acute hepatitis.[47] Hepatitis viruses, hepatotoxic drugs, and toxins are implicated in the possible etiology of this condition. Fulminant hepatic failure was more common among HEV-infected women (55%) who were 2.7 times at higher risk than non-HEV infected women (20%); maternal mortality was also higher secondary to fulminant hepatic failure in the HEV infected group (41%) vs. 7% in the non-HEV group.[48] This study highlights that HEV infection might be responsible for 2400 to 3000 stillbirths each year in developing countries, with many additional fetal deaths linked to antenatal maternal deaths.

Fulminant hepatic failure was significantly higher in pregnant women with HEV infection as opposed to other causes of acute viral hepatitis (69.2% vs. 10%, p<0.001). The prevalence and the severity of HEV infection in pregnant women did not differ significantly at various stages of gestation. It has been reported that a significant proportion of pregnant women with acute hepatitis E (up to 70%) progress to fulminant hepatic failure with high occurrence of disseminated intravascular coagulation.[5]

Mechanisms for High Morbidity of Hepatitis E in Pregnancy

Pregnancy is associated with high levels of steroid hormones. These steroid hormones may promote viral replication. It has a direct inhibition on hepatic cells, which may predispose to hepatic dysfunction when exposed to infectious pathogens.[49] Steroid hormones are immunosuppressive and mediate lymphocyte apoptosis through NF-κB. NF-κB have shown their primary role in liver development and regeneration. Prusty et al50studied the changes in NF-κB activity using electrophoretic assays of the p50 and p65 component in pregnant and non pregnant patients with fulminant hepatic failure (FHF) due to hepatitis B,C and E. They found that the activity of the p65 component of NF-κB was diminished in both the peripheral blood mononuclear cells (PBMC) and post mortem liver biopsy specimens in pregnant patients with fulminant liver failure.

Jilani et al[51] found that HEV infected pregnant women with fulminant hepatic failure had lower CD4 count and higher CD8 counts. They also observed that the levels of estrogens, progesterone and beta-hCG were significantly higher in the above-mentioned group when compared to HEV negative patients or control healthy pregnant females. Although the levels of hormones were physiologically high in the normal control population, patients with HEV infection seem to have significantly higher levels than controls, which probably explain the direct interaction of HEV with the immune system.[52]

Pal et al[53] studied the cellular immune response in both pregnant and non pregnant women with acute hepatitis E and the control population and found that pregnant women with HEV had generalized immune suppression characterized by decrease in lymphocyte response to phytohemagglutinin (PHA) with a predominant Th2 bias as compared to non pregnant women with hepatitis E and normal healthy controls.

This challenged the previously existing hypothesis that normal pregnancy is associated with systemic immune suppression with an increased risk of infections.[54] This study was important from a number of perspectives. The thought that normal pregnancy is an immunosuppressed state is challenged because normal healthy pregnant women did not demonstrate decreased response to PHA. Also, non-pregnant patients with HEV did not show any defective PHA response either highlighting that HEV by itself does not produce the immunological changes and needs a pregnancy as a physiological state to produce the above-mentioned changes. It has been suggested that a reduced expression of the progesterone receptor or a mutation of the human methylenetetrahydrofolate reductase (MTHFR) gene might be associated with development of fulminant hepatitis E in pregnant women.[55,56] An increased incidence of FHF was reported in pregnant women with the progesterone receptor gene mutations PROGINS haplotype. PROGINS carriers with HEV infection showed reduced expression of progesterone receptor and progesterone-induced blocking factor (PIBF). PIBF exerts its anti-abortive activity by inhibiting NK cells and influencing both the humoral and cellular immune responses.[57] In addition to the above mentioned factors, Khuroo et al[57] suggested that infection of the fetus with HEV may be responsible for the increased severity of the disease in the mother; Variations in the major histocompatibility complex (MHC) which mediate antigen presentation may also explain some of the difference in the mortality in different geographical areas in women infected with HEV. Women with fulminant hepatic failure (FHF) presented a reduced expression of toll-like receptor (TLR) 3/TLR7/TLR9, a type of PRR that plays a key role in the innate immune system, and have weaker phagocytic macrophages than women with acute viral hepatitis E. [58] Kumar et al. reported that high concentrations of cytokines (TNF-α, IL-6, IFN-γ and TGF-β1) may also be associated with an adverse pregnancy outcome. [59] Host factors such as nutritional status, which may affect and be affected by pregnancy, may also contribute to the immune response to HEV infection in pregnant women.[51] Complement system plays a key role in continuation of a healthy pregnancy and progression to a favourable outcome. Viral hepatitis leads to a dysregulation of the complement system that adversely affects the pregnancy.

Reduction in C3 and C4 concentrations in these patients may reflect complement consumption or reduced production due to a decline in the number of functioning hepatocytes. This hypothesis is supported by the simultaneous decrease in the concentrations of C4 and albumin, which are produced in the liver. Since the liver is the major site of synthesis of most of the complement components, the low serum complement level has been proposed to be induced by the defective synthesis of the components. These results indicate that patients with hepatic disease have severe complement depletion that is probably multifactorial in origin. This impairment in complement function may be returned to two mechanisms: a failure to synthesis a certain number of components and regulatory proteins of complement and an increased consumption due to activation of the complement system. The increase consumption theory was supported by several reports.[60] An association has been suggested between increasing severity of liver disease and increasing degrees of complement activation as shown by the C3d:C3 ratio being highest in patients with severe liver disease and by the correlations of C3d:C3 values with other markers of liver damage such as albumin, ALP and AST. The absence of an increase in complement during pregnancy suggests increased complement activation with generation of anaphylatoxins which drive poor placental vascularization and trophoblast injury.[61] Higher viral load of HEV has been reported to be associated with FHF during pregnancy; this was reported in a study by Kar et al., where a comparatively higher HEV viral load was observed in FHF patients (139994.0±103104.17 copies/ml) than AVH patients (768.92±1105.40 copies/ml).[55] High fetal mortality has been explained in AVH and FHF cases which showed vertical transmission of HEV from HEV infected mothers to their infants.[62] Kumar et al evaluated nutritional status clinically as well as biochemically (serum prealbumin and folate) in 144 pregnant women with HEV infection and 144 healthy asymptomatic age and gestational age-matched pregnant women as controls. It was concluded that malnutrition might confer a higher predisposition for HEV infection during pregnancy and is associated with increased severity of disease in terms of occurrence of ALF.[63]

Thus, a complex interaction of viral, host, immunological and hormonal factors with each other produce a paradigm of severe liver damage in pregnancy.

Maternal Outcome

Hepatitis E acts as a catalyst for coagulopathy that contributes to maternal morbidity and mortality. Postpartum hemorrhage (PPH) is the leading proximal cause of maternal death in developing countries.[64,65] HEV infection disrupts coagulation and this increases the likelihood of uncontrolled bleeding during the peripartum period. Women admitted to a tertiary care hospital in New Delhi, India, with acute HEV (n= 132) had significantly elevated prothrombin times relative to those of women admitted for other acute viral hepatitides (n = 88). [48] The HEV-infected women had a greater incidence of antepartum and postpartum hemorrhage , gastrointestinal bleeding, and therefore elevated maternal mortality. Puri et al.[65] conducted a case-control study in New Delhi in pregnant women in third-trimester with acute HEV Women with postpartum hemorrhage had approximately five times the odds of having experienced hepatic encephalopathy as women without PPH and had 20 times the odds of a gastrointestinal bleed, though only gastrointestinal bleeding remained a significant clinical predictor of PPH after controlling for other factors. Around one third of women admitted to the hospital with acute HEV infections experienced postpartum hemorrhage.[65] Other maternal complications include ascites, GI bleed, renal failure, seizures, disseminated intravascular coagulation (DIC), premature rupture of membranes, preterm labor, spontaneous abortions and death due to acute liver failure.[48]

Fetal Outcome

There is high risk to fetus in terms of low birth weight, small for gestational age and high morbidity due to preterm delivery. A recent study highlights that HEV infection might be responsible for 2400 to 3000 stillbirths each year in developing countries, with many additional fetal deaths linked to antenatal maternal death.[48] The clinical presentation in the neonate may be as hypothermia, jaundice, anicteric hepatitis, acute liver failure, recurrent diarrhea, fever or stillbirth.[42] Hypoglycaemia may occur, the liver function test abnormalities include elevated bilirubin alone, elevated aminotransferases or a combination of both. The diagnosis is made by the presence of IgM HEV antibody and/or HEV RNA positivity.

In a sporadic setting, among all pregnant women infected with HEV, still births have been reported in 54% and neonatal deaths in 17%[48] whereas in an epidemic, fetal deaths including intrauterine and neonatal deaths were reported to be 12.4% in HEV related AVH and 75% in HEV-ALF patients.[42]

Management

Acute viral hepatitis caused by HEV infection is usually self limiting and, in the absence of complications, does not require therapeutic intervention. In cases of uncomplicated viral hepatitis symptomatic treatment leads to improvement. Higher vigilance and close follow up is needed owing to its high rate of complications in pregnancy. Fresh frozen plasma is used in cases of active bleeding and deranged coagulation profile. Fulminant hepatic failure patients should be ideally managed in an intensive care unit, with continuous, noninvasive cardiac, oxygen saturation and blood pressure monitoring. Elective ventilation should be done for patients with grade IV encephalopathy and for those with grade III encephalopathy and evidence of cerebral edema. All patients should be started on prophylactic antibiotics for prevention of infection. The preferable mode of delivery is vaginal. Usually, the women go into spontaneous labor. There is a high incidence of preterm delivery; steroid cover is given for fetal lung maturity. Management of liver failure in pregnancy requires a combined and coordinated effort by the intensivist, obstetrician, hepatologist, neonatologist, and if necessary, the transplant team. Vitamin K supplementation should be given, preparedness to manage PPH, facilities for neonatal resuscitation, active management of third stage of labor in all cases is recommended. Post partum monitoring for vitals, bleeding, and neurological status is needed. Successful liver transplantation has been reported in pregnant females with acute liver failure.[67,68] It can be considered in selected cases.

Two recombinant subunit vaccines have undergone human trials, and a few others are under development.[69,70] One of the recombinant vaccines (Hecolin®) was licensed for use in China in 2012. It is composed of a truncated HEV capsid protein, p239, that confers protection against hepatitis E infection

for up to 4.5 years.[71] However, its safety in pregnancy is yet to be proven.

Conclusion

Hepatitis E is a leading cause of acute viral hepatitis, maternal death and wastage of pregnancy. Current understanding of HEV transmission indicates that effective prevention and control depend on ensuring a safe drinking water supply, adequate sanitation, and proper personal and environmental hygiene. However, in settings where hepatitis E outbreaks occur, it is essential to ensure adequate prevention measures in a timely manner in view of rapid transmission of HEV and high morbidity of disease.

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Original Article: Obstetrics

Postpartum Collapse – A Complication of Preeclampsia and Eclampsia

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ABSTRACT

Background: Collapse following delivery in preeclampsia and eclampsia is not always accounted for by postpartum hemorrhage. Disturbance of steroid metabolism and electrolyte imbalance have also been reported to cause postpartum collapse.

Objectives: i) To study the clinical and biochemical parameters in cases of preeclampsia and eclampsia developing postpartum collapse with postpartum hemorrhage and without postpartum hemorrhage ii) To observe the response to therapy in both the groups. iii) To formulate emergency treatment plan for these cases.

Materials and Methods: Postpartum collapse manifested shortly after delivery (within 6 hours) was studied with regards to clinical parameters and investigations including study of electrolytes.

Results: Out of 26 cases of preeclampsia and eclampsia with postpartum collapse, 14 had low serum sodium and high potassium whereas 12 cases had acute severe blood loss. All patients without PPH treated with 0.9% sodium chloride (4 cases), 3% hypertonic saline (10 cases), and all but 3 cases of PPH receiving blood transfusion had remarkable improvement. Only 3 cases of maternal deaths were reported, all with PPH due to non-availability of blood in one case and irreversible shock on admission in 2 cases. Conclusion: Emergency treatment in the form of sodium chloride or blood transfusion early may be decided on clinical judgment even when laboratory backup facility is not available. Early treatment is needed to save the cases of postpartum collapse.

Keywords: Postpartum collapse, Preeclampsia, Eclampsia, Electrolytes, Postpartum hemorrhage

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Introduction

Among the various postpartum accidents and hazards described in the literature, shock is the commonest manifestation and is usually due to acute blood loss. Changes in electrolyte balance and steroid metabolism may also result in shock like states especially in the postpartum period when there is profound adjustment and alteration in the electrolyte and steroid system.[1] Causes of Postpartum collapse has been elaborately discussed by N.Al-Shabibi & L. Penna.[2]

Postpartum vasomotor collapse is a serious complication of preeclampsia, occasionally after vaginal delivery and more commonly after caesarean section, and it may occur within the first 24 hours postpartum.[3]

Bailey[4] in 1911 reported the first series of cases of this shock like state and attributed profound shock and drop of blood pressure to rapid emptying of the uterus in eclamptic patients. Simon and Rasmussen[5] observed a drastic fall of blood pressure after delivery in preeclamptic mothers. Adair et al[6] concluded that toxemia was the most important etiological factor with delivery precipitating the onset of vascular collapse.

Because of the relative rarity of the complications, its basic nature has remained poorly understood. Electrolyte disturbance in the form of low sodium and chloride and raised potassium has been attributed to its etiology by Tatum and Mule.[7,8] Hypovolemia is another cause of postpartum circulatory collapse in preeclmapsia and eclampsia with normal hematocrit before delivery, developing collapse despite a normal estimated postpartum blood loss.[3]

Pathophysiology and management of preeclampsia associated severe hyponatremia has been reported in case reports by Sandhu et al.[9] Hyponatremia in patients with preeclampsia may be associated with increased risk of maternal seizures, and foetal sodium level of less than 130mEq/l can cause fetal jaundice, tachypnea, seizures and polyhydramnios. The patients with worsening neurological signs and symptoms may be started with 3% hypertonic saline immediately with urgent delivery.[9]

Awareness and frequent monitoring of hyponatremia should become an integral part of monitoring of women if preeclmapsia.[10]

Objectives

i) To study the clinical and biochemical parameters in cases of preeclampsia and eclampsia developing postpartum collapse with postpartum hemorrhage and without postpartum hemorrhage
ii) To observe the response to therapy in both the groups.
iii) To formulate emergency treatment plan for these cases.

Materials And Methods

Twenty six cases of postpartum collapse both with severe preeclampsia and eclmapsia were taken up for the study at Bankura Sammilani Medical College and Hospital and also at North Bengal Medical College and Hospital between March 1998 and February 2008.

It was a prospective, observational, clinical study.

Detailed history was taken from the relatives and thorough examination (both general and obstetrics) was done particularly noting the age, gravida, parity, place, mode of delivery and gestational age at delivery. Blood pressure during pregnancy was noted and frequent observation were made of consciousness, blood pressure, respiration, urine output and bleeding per vagina at 15-60 minutes intervals in the collapsed patients depending on the maternal condition. Blood sample was drawn at the time of starting IV infusion while starting the management. Investigations advised was for Hb%, peripheral smear, platelet count, renal function test, liver function test, sodium and potassium estimation.

Estimated blood loss of more than 500 ml were considered for blood transfusion and less than 500 ml were infused 0.9% sodium chloride in 4 cases and 3% hypertonic saline in 10 cases. Serum Sodium and potassium estimation was done at the collapsed state and repeated 6-8 hours post-therapy. The response to therapy, hospital stay and condition on discharge were noted.

Results

The total number of patients in the study was 26 (Group A – postpartum collapse without PPH – 14 cases; Group B – postpartum collapse with PPH –

12 cases). The clinical profiles are shown in Table 1, majority were young primi gravida. Group A patients comprised 9 cases of preeclampsia, 3 cases of eclampsia and rest 2 superimposed preeclampsia.

In both the groups delivery collapse interval was 1 hr 54 minutes (range 40minutes to 4hours) and it persisted for 2 hours and 3 minutes (range 1hour to 3 hours and 16 minutes) showing no significant differences in the 2 groups.

Table 1: Clinical profiles of preeclampsia and eclampsia patients in the study

Profiles	GRA – Collapse without PPH (n =14)	GRB - Collapse with PPH (n = 12)
Religion		
• Hindu	6	4
• Muslim	8	7
• Others	-	1
Age		
• < 20	8	6
• 20-30	6	4
• > 30	-	2
Gravida		
• G1	8	5
• G2 – G4	4	6
• ≥ G5	2	1
Hypertensive types		
• PE	9	5
• ECL	3	6
• HTN with superimposed PE	2	1
Places of delivery		
• Pr / Sec Care Centre	2	8
• Tertiary care Centre	12	4
Type of delivery		
• Normal	8	6
• Forceps	4	2
• CS	2	4
Anesthesia for CS		
• SP	-	2
• GA	2	2

Restoration of blood pressure to stable level was observed concomitantly with administration of sodium chloride solution in Group A patients. On an average, each patient was infused with 1 liter of 0.9% sodium chloride in 4 cases and 3% hypertonic saline in 10 cases within a period of 85 minutes. Recovery was observed at about 32 minutes on an average, after the start of infusion. The first 500 ml was infused rapidly at 13 ml/minute and the rest 500 ml slowly at 8ml/minute. Of the group B patients 5 were infused with 3% sodium chloride when they did not recover with 2-3 units of blood transfusion. They also improved like Group A patients.

Clinical parameters at the collapse state are shown in Table 2.

Serum electrolytes at the collapsed state and 6-8 hours post-therapy are shown in Table 3. The significant drop of sodium in group A and recovery with sodium chloride was noticeable. Group B patients recovered with replacement of blood with additional need of sodium chloride in 5 cases.

Table 3: Serum electrolyte status in the study group

Groups	No of patients	Electrolyte concentration (mEq/L)			
		Na+		K+	
		AV	Range	AV	Range
Group A At collapsed state (0-4 hrs postpartum)	14	121.22	114.2-127.6	5.35	4.9-5.8
6-8 hrs post therapy	14	131.6	128.7-135.0	4.97	4.9-5.2
Group B At collapsed state	12	32.2	130-138	4.4	4.2-4.8
6-8 hrs post therapy	12	134.8	130-140	4.5	4.2-4.8

AV: average

Individual electrolyte parameters in Group A are shown in Table 4.

Three patients in the study (all of group B) died. In 1 patient blood loss was more than 1500ml and immediate blood transfusion could not be arranged because of her rare blood group. Two other patients reached our hospital from peripheral centers with irreversible shock and they expirad due to multiorgan failure.

Discussion

Acute blood loss, electrolyte imbalance and disturbance in steroid metabolism may cause shock like state in the postpartum period[1] and is a serious complication of preeclampsia.[3] We had similar observation of postpartum collapse due to PPH (12 cases) and due to electrolyte imbalance (14 cases).

Postpartum vascular collapse following delivery of preeclampsia was observed within 24 hours postpartum by Arias.[3] Our observation of 40 minutes agrees to this observation.

Tatum[7] observed low sodium and chloride along with high potassium in cases of postpartum collapse in

Table 2: Clinical status of the patients at collapsed state and post therapy

Profiles	GR. A – Collapse without PPH (n = 14)				GR. B - Collapse with PPH (n = 12)			
	At collapsed state		Post therapy		At collapsed state		Post therapy	
	AV	Range	AV	Range	AV	Range	AV	Range
Pulse	122	116-130	102	96-110	128	120-140	96	92-100
BP • S • D	 96 56	 88-100 52-68	 150 100	 140-170 92-106	 92 60	 86-98 56-70	 144 96	 138-160 90-100
Blood loss (ml) 200-500ml > 500 ml	 10 4				 12			

AV: average

preeclampsia patients, not associated with significant acute blood loss. We had 14 cases with similar observations. Response to infusion of 0.9% and 3% sodium chloride and repeat electrolyte level 6-8 hours post-therapy confirmed the hypothesis. We had 5 cases of postpartum collapse with PPH who did not recover with blood transfusion but responded to subsequent infusion of 3% sodium chloride. These patients had both the problems.

Delayed arrival and irreversible shock led to deaths in three cases of our series. These cases invite decision for empirical early treatment with blood transfusion and or sodium chloride in desperate cases when laboratory facilities are not available. Kalur et al[11] observed postpartum mobilization of fluid and sodium from extravascular space is delayed in some preeclampsia patients whose survival is unlikely unless there is rapid infusion of hypertonic or isotonic saline as is also stressed by Tatum.[8]

Summary and Conclusion

Postpartum collapse in preeclampsia and eclampsia in the study was either due to electrolyte imbalance (low sodium, high potassium in 14 cases) or to PPH (12 cases). Electrolyte imbalance quickly responded to sodium chloride infusion whilst the PPH group recovered with blood transfusion. Emergency treatment in the form of sodium chloride or blood transfusion early may be decided even when laboratory backup facilities are not available. Early treatment is needed to save the cases of postpartum collapse.

Conflict of Interest: There is no conflict of interest with this study.

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Original Article: Obstetrics

Second Trimester Ultrasonographic Determination of Umbilical Cord Coiling Index and Its Correlation with Perinatal Outcome

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ABSTRACT

Objective: to study the association between antenatal umbilical coiling index (aUCI) and perinatal outcome.

Methods: 150 primi gravida women with uncomplicated singleton pregnancy had an ultrasonography between 18 and 26 weeks of gestation to measure umbilical cord coiling index. The antenatal umbilical cord coiling index was calculated as a reciprocal value of the distance between a pair of coils (aUCI = 1/distance in cm) and was correlated with the following adverse perinatal outcome – 1) preterm labor, 2) Small for gestational age, 3) Meconium staining of liquor, 4) Non reassuring fetal status in labor, 5) Mode of delivery, 6) Admission in NICU. Statistical analysis was done by Chi –Square test.

Results: in our study normal UCI value was between 0.17-0.48. UCI value less than 0.17(less than 10th percentile) was taken as hypocoiled cord and UCI value more than 0.48 (more than 90th percentile) was taken as hypercoiled cord. Mean UCI was 0.32±0.08. Among the 150 women 118 (78.7%) had normal coiling index, 19 (12.7%) had hypocoiling and 13 (8.7%) had hypercoiling. Hypercoiling of the cord was significantly associated with small for gestational age neonates. Both hypercoiling and hypocoiling were found to be significantly correlated with preterm delivery, meconium staining of liquor and non reassuring fetal heart rate status and subsequently there was increased incidence of cesarean section.

Conclusion: Abnormal coiling index detected in second trimester by ultrasound is associated with small for gestational age neonates, preterm birth, meconium staining of liquor and non reassuring fetal heart rate status. So, antenatal UCI can be used as a predictor of several adverse perinatal outcomes.

Introduction

Umbilical cord is the lifeline that connects mother with the fetus. Its function is to protect blood vessels that carry oxygen and nutrients to the fetus. So, any compromise to the blood flow of the umbilical vessels may jeopardise the life of the growing fetus. It consists of 2 arteries and 1 vein and has characteristic screw shaped coil. The cause, role and the mechanism of

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the coiling is unknown,[1] but this helical structure of the vessels may be a protective mechanism of nature to resist obliteration of blood flow due to external compressive forces and mechanism may be related to early fetal activity and hemodynamic factors or anatomical issues such as presence of Roach muscle.[2,3] The helical pattern of the umbilical vessels was first described by Berengarious in 1521.[4] In 1954 umbilical cord coiling was first quantified by Edmonds.

The umbilical coiling index is measured by dividing the total number of umbilical vascular coils by the length of the cord in centimetres.[9,10] A coil is defined as a complete 360° spiral course of the umbilical vessels around whartons jelly.[11]

UCI = Total number of coils /Total length of the cord in centimetre

<10th percentile= hypocoiled
10th – 90th percentile = normocoiled
>90th percentile = hypercoiled.

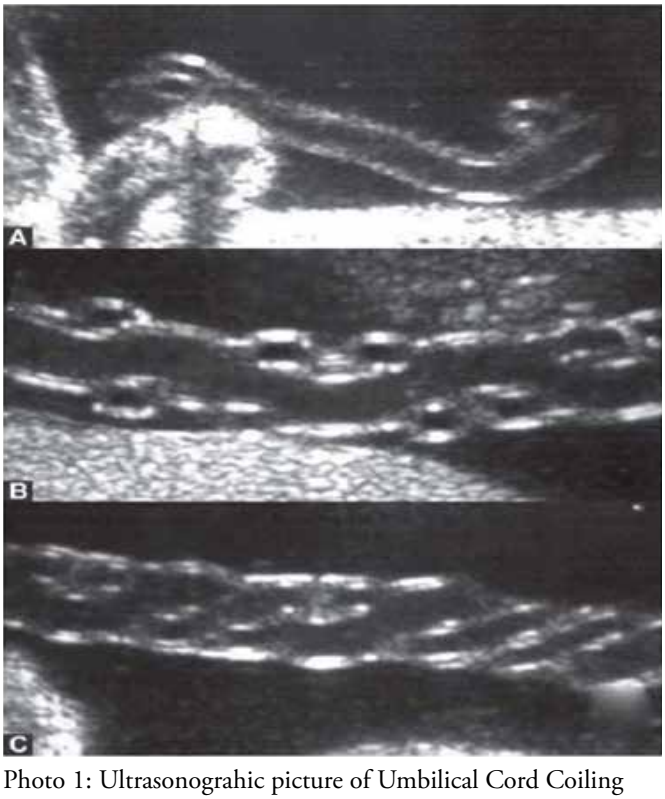

Photo 1: Ultrasonograhic picture of Umbilical Cord Coiling
A : Hypocoiled Umbilical Cord
B : Normocoiled Umbilical Cord
C : Hypercoiled Umbilical Cord

Normal coiling index is approximately 1 coil/5 cms of umbilical cord length. Antenatally coiling can be measured by ultrasound.[8] Antenatal UCI is calculated as a reciprocal value of the distance between a pair of adjacent coils measured in cms from the inner edge of an arterial or venous wall to the outer edge of next coil along the ipsilateral side of umbilical cord, the direction being from placental end to foetal end.[9] The final value is the average of three readings at three different segments of umbilical cord. Abnormal coiling is defined as hypocoiled or hypercoiled umbilical cord with corresponding UCI values <10th or > 90th percentile respectively.[9,10] Abnormal coiling is associated with preterm birth, small for gestational age (SGA), meconium staining of liquor (MSL), non reassuring foetal heart rate status (NRFS) and subsequently there are higher rate of emergency caesarean section and admission in NICU.[6,7] Hence antenatal measurement of UCI can help to detect fetuses at risk and to do necessary intervention if required.

Method

A prospective observational study was conducted in Vivekananda Institute of Medical Sciences, Kolkata to assess the correlation between umbilical coiling index and adverse perinatal outcome.150 booked primi gravida women with singleton pregnancy attending regular antenatal check up and willing for institutional delivery were included in the study randomly. Pregnancy with medical and surgical complications like diabetes, hypertension, obstetric cholestasis, thyroid disorder etc were excluded from the study. Umbilical coiling index was measured between 18 and 26 weeks of gestation by ultrasound. Later they followed up till delivery and adverse outcome was assessed by incidence of SGA neonates, preterm delivery, meconium staining of liquor, non reassuring fetal heart rate status, rate of cesarean section and admission to NICU.

The percentile values of antenatal UCI were calculated. Results were analysed using Chi – Square test to see the association between different study variables. P≤0.05 was considered statistically significant.

Result

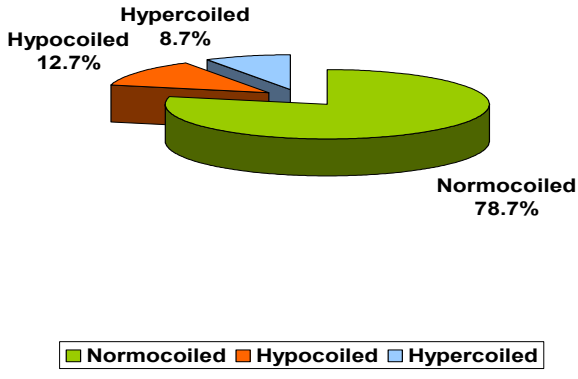

Figure 1: Distribution of the patients according to aUCI

Out of 150 women 118 (78.7%) had normal coiling index, 19 (12.7%) had hypocoiling, and 13 (8.7%) had hypercoiling. In our study 10th percentile value was 0.17 and 90th percentile value was 0.48. So aUCI values of normocoiled group is between 0.17 and 0.48, hypocoiled group is less than 0.17 and hypercoiled group is more than 0.48. Both hypocoiling and hypercoiling of the cord were found to be significantly correlated with preterm delivery, meconium staining of liquor, non reassuring fetal heart rate status and subsequently there was increased incidence of cesarean section. Hypercoiling of umbilical cord was significantly associated with SGA neonates and higher admission in NICU at birth.

Discussion

The helical twisting of umbilical cord plays an important role in the protection of its fragile vascular system.[8] The UCI can therefore become a promising marker of adverse perinatal outcome which has been observed by previous studies.[4,5]

The mean UCI in our study was 0.32±0.08 and the 10th and 90th percentile of UCI were 0.17 and 0.48 respectively. These values were in agreement with few of the previous studies.[10,11] The mean UCI of 0.32±0.08 is somewhat higher as compared to 0.20±0.10 reported by Ercal et al,[11] 0.21±0.07 by Strong et al[5] and 0.19±0.10 by Rana et al,[12] 0.13±0.10 by S. Gupta et al[4] but lower than the mean UCI values of 0.62±0.20, a study by Qin et al.[10]

In our study, we observed significant association between hypercoiling of umbilical cord and SGA neonates at birth. Similar result has also been reported by de Laat et al.[13] and Nishio et al.[14] but Predanic et al15 and S Gupta et al4 in their studies have shown that both hyper and hypocoiled umbilical cord were associated with SGA neonates.

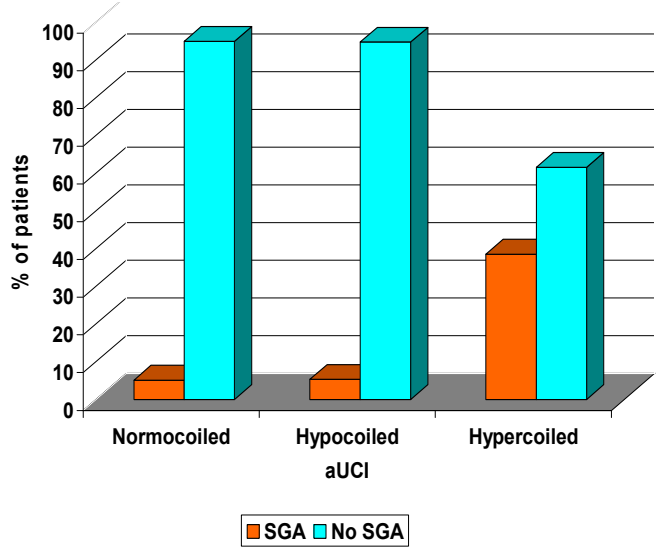

Figure 2: Correlation of aUCI with SGA neonates among the patients

In contrast to the study by Predanic et al[15] and S Gupta et al[4] our study found significant correlation between abnormal coiling pattern and preterm delivery. de Laat et al[13] has reported a higher incidence of preterm delivery in undercoiled cords whereas Rana et al[12] found premature delivery to be more associated with overcoiled cords.

Our study found significant association of abnormal coiling of umbilical cord with presence of meconium stained liquor and non reassuring fetal heart rate status. This was in concordance with findings reported by S Gupta et al[4] and Predanic et al[15] whereas significant association of meconium staining of liquor with hypocoiling has been reported by Ballard et al.[16]

Our study therefore confirms few of the findings of previous studies. One major limitation of our study is the limited number of cases. Secondly there was lack of proper randomization. Sometimes it was difficult to measure UCI by ultrasound specially in cords with very irregular coiling pattern. Sometimes there could be sonographic error on the part of observer. Nevertheless, an abnormal UCI diagnosed by USG in the second trimester of pregnancy can help to

predict adverse perinatal outcome and lead to proper intervention at right time.

Conclusion

We conclude from our study that hypercoiling of umbilical cord is associated with SGA neonates and abnormal coiling index (both hypercoiling and hypocoiling) is associated with meconium staining of liquor, non reassuring fetal heart rate status etc.So abnormal coiling pattern of umbilical cord visualised by sonography can be used potentially as a predictor of several adverse perinatal outcome which may be helpful in picking up fetuses at risk and appropriate preventive measure can be taken so that every pregnancy ends in a healthy mother and healthy baby.

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Case Report

Infertility : an Underdiagnosis of Genital Tuberculosis

Dr Chandrachur Konar,[1] Dr Roshini P,[2] Dr Sukanta Bhuiya,[3] Dr Rudri Bai,[4] Dr Rajiv Kumar Saxena,[5]

ABSTRACT

Although the relation between genital Tuberculosis (GTB) and Infertility has been well established, but for an asymptomatic lady, the diagnosis requires a very high index of suspicion. Timely diagnosis and appropriate treatment can successfully prevent infertility / subfertility or its sequale. Though genital Tuberculosis is always secondary to a primary foci, CA 125 value, Adenosine deaminase levels (ADA), biopsies, curettings or aspirate for histopathological examinations for granulomatous lesions and also AFB smear and culture or BACTEC systems are necessary for accurate diagnosis. Complete blood count, ESR, Mantoux test, Chest X-ray and sputum for AFB needs to be done for a suspected case. We report here a patient with 6 years infertility that was discovered to have genital tuberculosis following a laparotomy for a pelvic mass and a histologic diagnosis of TB.

Introduction

Tuberculosis is a major health problem throughout the world which affects about 9.4 million people annually causing around two million deaths. India and China together account for 40% of the world's TB burden. Co-infection with human immunodeficiency virus (HIV), more liberal immigration from high risk to low risk areas due to globalization has been responsible for increased incidence all over the world. Multidrug resistant (MDR) and extreme-drug resistant TB (XDR) cause serious concern.

Other than the commonest and the most infectious pulmonary TB, extra-pulmonary TB (EPTB) is on gradual increase globally. Female genital TB (FGTB) continues to be an important cause of significant morbidity, especially infertility/subfertility. The disease may masquerade as other gynecological conditions—details.Timely diagnosis and prompt treatment can successfully prevent infertility and its sequelae.

Case Reports

Patient: Mrs. S, 24 yrs, Nulligravida, married for 6 years attended OBG casualty at MVJ MC and R H with the complains of Amenorrhoea for 6 weeks, Spotting P/V for 14 days and Pain lower abdomen for 5 days. UPT was Negative. Her pain was colicky type, not associated with fever, loose stools, vomiting or syncope. **Menstrual History:** Her previous cycles were regular, not associated with clots or dysmenorrhoea. No history of inter menstrual bleed, dyspareunia, or post coital bleed. Not on any contraceptives. She had taken 3 cycles of OI. No reports were available. **On Examination:** Patient was alert, conscious, in acute pain, afebrile, hydration apparently maintained with

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moderate pallor. No lymphadenopathy. BP: 110/70 mm Hg;P : 110 beats / min.CVS / RS: Clinically NAD. **Per Abdomen:** Abdomen was acutely tender over RIF & supra pubic region. Muscle guard was present. Abdomen was not distended. No mass was palpable. **Per Speculum:** Cervix and vagina healthy. External os was closed. No discharge/bleeding per vagina. **Bimanual Examination:** Uterus was normal in size. Cystic mass palpable in right fornix which was tender. Uterus was deviated to left side. **Investigations:** USG report showed: 1) Right adnexal Dermoid cyst measuring 6.1 x 5.8 x 4.9 cms with Torsion. 2) Right sided Pyosalpinx 3) Another mass of 7.5 x 5.2 x 4.6 cms with volume of 95 cc noted lateral to the Dermoid cyst. Hb:8 gm%. Emergency laparotomy was done. Intra op: Right ovarian multiloculated cyst of 8 x 7 cms with one and half turns of torsion at the pedicle. Cyst containing hair and sabeceous material. Right sided pyosalpinx of 5 x 3 cms present. Left ovary Normal. Adhesions of Right tube with small bowel and peritoneum was found. Uterus normal. POD adhesions were present. Procedure done: Emergency Laparotomy with Right Ovarian Cyst detorsion and Cystectomy with Right Salpingectomy with adhesiolysis in pelvis and POD.

Considering the laparotomy findings and considering the infertile status of the patient, Endometrial sampling was done for HPE and sent for TB – PCR. **TB-PCR report:** Positive for mycobacterium TB complex. **HPE:** Dermoid cyst of the ovary, with pyosalpinx. **Endometrial biopsy:** Caseation necrosis present. Further investigations for TB were planned like Sputum Culture, CXR, Mantouxtest; **Sputum for AFB:** No growth. **CXR:** NAD; **Mantoux test:** No induration after 48 hrs. Postoperative recovery was uneventful. Patient was diagnosed as extra pulmonary genital tuberculosis / female genital tuberculosis and started on CAT I Anti Tubercular Treatment (ATT); and is currently on the same.

Discussion

Frequency of Genital TB among OBG patients: 1) Pulmonary TB: 24%. 2) Secondary Amenorrhoea: 9.3 %. 3) Infertility: 03 %. 4) DUB: 1.5 %. 5) Ectopic pregnancy sacs: 1.5 %. 6) Hysterectomy Specimens: 1.0 %. Major female population affected with Tuberculosis are infertile. Incidence of infertility amongst TB infected individuals range from 44 % (Sutherland ; n=711) to 58 % (Tripathy ; n=290). Others being: Amenorrhoea, Post Menopausal bleed, Pelvic pain etc in decreasing orders.[1] Majority of women affected are in the reproductive age group. Approximately 75% in 20-45 years.[2] However, the symptoms remain asymptomatic in a vast majority. Less vascularity of female genital organs, decreased oxygen tension, along with cessation of hormonal influence leading to atrophy of endometrial tissue contribute to low presence of the disease in the elderly. Pelvic mass may be silent fully and adnexal tenderness may be elicited. Pelvic mass is thought to be one of the significant signs of Genital TB.[3] Genital Tuberculosis is responsible for 5% of all pelvic infection.[4] Worldwide incidence of female Genital TB in Infertile population has been reported as 5-10%.[5,6] Range varying of under 1% in USA to about 10% in India.[5,6] Extra Pulmonary Tuberculosis: The term Extra Pulmonary Tuberculosis (EPTB) is used to describe isolated occurrence of tuberculosis at sites other than the lung. Incidence of EPTB by site:[7] 1) Lymph Node: 47%. 2) Pleural Effusion: 30%. 3) Abdomen: 10%. 4) Bone: 8%. 5) TB Meningitis: 2%. 6) Others: 3%. Genital organs most commonly affected are:[8] Fallopian Tubes: 100%. (Ampulla > Isthmus > Interstitial), Endometrium: 50-60% and Ovaries: 20-30%. Infection to genital tract is almost always secondary to primary focus mainly in lungs. The spread is mostly by hematogenous route (90%). Lymphatic spread, direct extension (from adjacent abdominal organs) or sexual transmission (from an infected partner) can occur rarely.

Adnexal lump of genital TB needs to be differtiated from chronic ectopic pregnancy, ovarian malignancy, endometriosis and chronic PID.

Diagnosis is often difficult. Complete Blood count, ESR, Mantoux test, Chest X-ray and sputum for AFB should be done in a suspected case.

Endometrial biopsy, curettings or aspirate in the premenstrual phase for histopathological examination (in formalin) for granulomatous lesions and also for AFB smear and culture (in normal saline) by conventional (L-J media) or BACTEC system is the gold standard method for diagnosis. Menstrual Blood culture on 1st day of period can also be done.

PCR test for mycobacterial DNA is a rapid adjunctive diagnostic tool with high sensitivity (90%) and

speficity (80-90%). It may be positive in presence of as low as 1-10 organism per ml. It can be done with menstrual blood on 1st day, with endometrial aspirate or curettings. However, because of insufficient reliability, treatment can not be started or stopped on the basis of PCR test.

Treatment is medical with Anti Tubercular Drugs (ATD). Genital TB is treated under CATEGORY I comprising of an intensive phase with Rifampicin, Isoniazid, Pyrazinamide and Ethambutol for 2 months and a continuation phase with rifampicin and isoniazid for next 4 months.

Surgical management is rarely needed for women with persitant Tubo-ovarian mass /abscess. Total abdominal hystectomy with bilateral salpino-oophorectomy is the option in parous women. Drainage of pelvic or tubo-ovarian abscess may also be done followed by ATD. New TB Research: New and improved BCG vaccines are being developed. New drugs, effective against strains that are resistant to conventional drugs and requiring a shorter treatment regimen are being developed. By controlling TB, FGTB can also be kept at bay and treated early to prevent development of short term & long term sequale of this menace.

Conclusion

GTB is a chronic disease presenting with infertility in the majority of women. There is underestimation of the GTB largely because it can exist without any clinical manifestation, has diagnostic difficulties and unfortunately the screening of GTB is not yet considered part of the infertility and menstrual dysfunction work-up in many centers. Because of the silent nature of GTB, which allows development of fulminating disease, the conception rate is very poor and therefore, early diagnosis and treatment is vital to improve outcome.

Conflict of interest

There is no conflict of interest with this study.

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Case Report

Successful Pregnancy Outcome in a Case of Evans' Syndrome during Clinical Remission Phase

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Introduction

Evans' syndrome (ES) is a rare hematological condition defined as immune thrombocytopenic purpura and immune hemolytic anemia, in which separate antibodies are directed against platelets and red blood cells. Immune hemolysis may be induced by alloantibodies directed against transfused red blood cells. Direct coombs test is a major tool for diagnosing this disorder. Common causes of immunologic thrombocytopenia are viral or bacterial infections, drugs and autoimmune idiopathic thrombocytopenic purpura. Women usually presents with anemia, menometrorrhagia and splenomegally. Thrombocytopenia may persist for many years. Few cases of evans' syndrome with pregnancy was reported as of now. It runs a more benign course in pregnancy than Sin non pregnant state and very often resolves post-delivery.[1] We present a case of Evans' syndrome in clinical remission with a successful pregnancy outcome of both mother and baby.

Case Report

A 24 year old female G1, p0+0, was admitted to our hospital with complaining of 38 weeks pregnancy and watery discharge per vaginum since last 24 hours. On examination she was not pale, BP was 130/70 mm of mercury, uterus- fundal height 34 weeks with scanty liquor, FHS 156 per minute, regular and internal os admits tip of finger. She conceived with IUI three times for oligospermia of her husband. During her antenatal period she did regular check-up, total pregnancy weight gain was 10kg. She had mild preeclampsia controlled with labetalol.

During pregnancy her blood reports were Hb-12.2gm/dl, platelet count 245000/cmm, serum bilirubin 1.7mg/dl. Counselling was done and she consented for cesarean section and an alive healthy baby, weigh 2600gm was delivered. Post partum was uneventful, no PPH occurred, mother and baby discharged after 7 days with advice for follow-up visits. Baby's blood reports were Hb 16.40gm/dl, platelet count 259000/cmm, WBC 17300/cmm, RBC morphology normochromic normocytic. In the postpartum period patient's blood reports were Hb 10gm/dl, platelet count 222000/cmm, TLC 9900/cmm, LDH 171u/l, reticulocyte count 3% and routine urine reports were normal. USG of whole abdomen done in the post partum period showed mild hepatomegaly, splenomegaly and periportal lymphadenopathy.

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Placental histopathology were consistent with termed mature placenta.

She was diagnosed in 2007 as autoimmune hemolytic anemia and idiopathic thrombocytopenic purpura with iron deficiency anemia. She was advised tablet iron, azathioprine (50 mg) and prednisolone (40mg) daily. After treatment she went into clinical remission. She wanted then to become pregnant and therefore azathioprine and prednisolone were stopped and her blood reports at that time were Hb 10.8gm/dl, TLC 5000/cmm, Platelet count 90000/cmm, Direct coombs test 3+, LDH 299 u/l. She was in clinical remission during the antenatal and post partum period. Thereafter she had fever with low Hb 4.3gm/dl, raised bilirubin, mild raised liver enzyme and she received 5 units of blood transfusion. No history of bleeding from any site, breathlessness, swelling anywhere, headache, loose motion, vomiting, visual or hearing impairment. Azathioprine and low dose prednisolone again started and she was informed that she may require spleenectomy if there is deterioration or relapse, again after stopping treatment.

Discussion

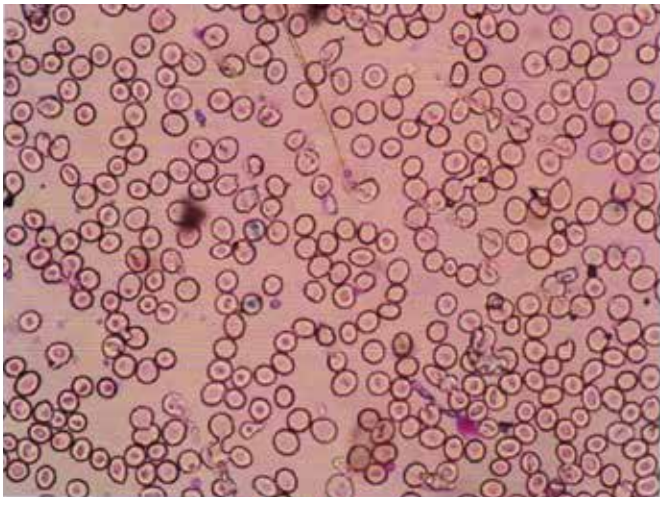
Autoimmune hemolytic anemia occurs at all ages, most reported during adulthood in women and presents with menometrorrhagia with immune thrombocytopenia. Evans syndrome diagnosed before pregnancy, most reported during childhood. It is a chronic hematologic condition usually presented with anemia and thrombocytopenia for which some sorts of treatment required and pregnancy is contraindicated. Typically, the disease runs a chronic course characterized by relapse and remissions. In the present case since her diagnosis of ES she was on azathioprine and prednisolone daily and her disease was in clinical remission. As she planned for pregnancy azathioprine and prednisolone were stopped. The occurrence of thrombocytopenia may coincide with the hemolysis or may arise as separate episodes. The platelet and red cells antibodies are distinct and do not cross react.

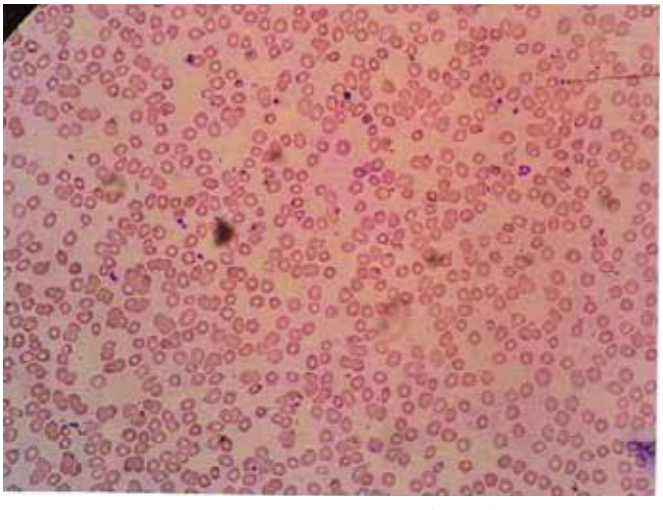
Management of pregnancy complications include abruption of placenta, APH, PPH, severe anemia and fetal intracranial hemorrhage, neurological damage, IUFD. No antenatal measure can reliably predict the fetal and neonatal platelet status, platelet antibodies can pass through the placenta and bind to the fetal platelets resulting in fetal thrombocytopenia.[2] In the present case antenatal check-ups were normal with adequate weight gain and fetal biometry were normal. Development of mild preeclampsia was well under-controlled with labetalol. Cesarean section was done and a healthy baby delivered at term. No PPH occurred and no blood transfusion required throughout antenatal and post natal period. Mode of delivery in women with ES depends on obstetric indications and hemorrhagic complications have not been shown to be related to the mode of delivery.[3] Treatment has been recommended for women with platelet count below 10000/μl at anytime during pregnancy, or below 30000/μl in the second or third trimester or when associated bleeding. With appropriate treatment, women with Evans' syndrome can have successful pregnancies, with a good response to conventional treatment.[1]

In the postpartum period, neonate may develop severe hemolytic anemia and moderate to severe thrombocytopenia. In our case baby was doing well during that period and investigations were normal. Mother was doing well till one year after delivery. She breast fed her baby for one year, not used any oral contraception and her menstruation cycle was regular. Thereafter she again presented with anemia, jaundice and spleen was palpable 5cm below the left costal margin for which azathioprine and prednisolone again started, blood transfusion given. Splenectomy removes a primary site of sequestration as well as a major site of antibody production. Other treatment used for ES include cyclophosphamide, danazole, vinka alkaloids, plasmapheresis. Intravenous gammaglobuline used when rapid correction of hemolysis is required and to raise the platelet count temporarily prior to surgery or labor and delivery. More recently, the anti-CD20 antibody rituximab has produced remission of both cytopenia in a high proportion of children and adults with steroid refractory Evans syndrome. Stem cell transplantation offers the only hope for long term cure for severe refractory patients but carries a significant risk of transplant- related morbidity and mortality.

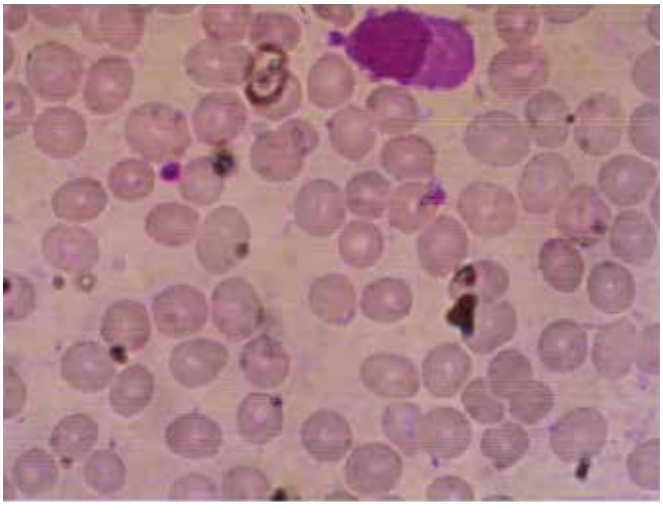
Conclusion

Evans' Syndrome is a rare disorder, requires medical treatment during which where pregnancy is contraindicated. During the clinical remission period she conceived with IUI and pregnancy was uneventful





Photograph 1&2: Showing recent blood film of mother (RBC- microcytic hypochromic with fragmented cells and platelets are adequate)



Photograph-3: Peripheral blood film of baby showing RBC- predominantly normocytic normochromic, WBC- within normal limits and platelets are adequate.

except development of mild preeclampsia. Though there were major complications reported during pregnancy and post partum period, in our case a healthy baby delivered by cesarean section and both mother and baby were doing well till one year after delivery. Evans' Syndrome relapses again thereafter, for which she is on azathioprine and prednisolone now, and she may require splenectomy in future.

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