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Contents

Tuberculosis in Female Genital Tract – Revisited

Female genital tract tuberculosis is one of the most obscure pelvic condition which poses diagnostic dilemma in clinical practice.

The global prevalence of Genital tuberculosis is estimated to be 8-10 million cases. The incidence is rising in resource poor countries due to its association with HIV. Genital TB represents 9% of all extrapulmonary TB. India has been accountable for one fifth of the global incidence of TB annually. Therefore, a significant number of genital TB is expected in India. The data in this regard is very limited.

Tuberculosis is caused by Mycobacterium tuberculosis. Infection to genital tract is almost always secondary to primary focus mainly in lungs. The spread is mostly by hematogenouus route (90%). Lymphatic spread, direct extension (from adjacent abdominal organs) or sexual transmission (from an infected partner) can occur rarely.

The commonest site of infection are the fallopian tubes (90-100%). The other sites are endometrium (50-60%), ovaries (20-30%), cervix (5-10%), vagina and vulva (1-2%).

Commonest presenting symptom is subfertility. Menstrual dysfunction in the form of amenorrhea or hypomenorrhea can also occur, Menorrhagia can be a presenting feature in early endometrial TB. Women may present with chronic pelvic pain or lump abdomen. Many of the women are asymptomatic.

On clinical examination, signs are often vague. Poor general health, ascites, adnexal lump may be found. Adnexal lump of genital TB needs to be differentiated 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 needs to 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 specificity (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 cannot be started or stopped on the basis of PCR test.

Genital TB may be suspected during laparoscopy (caseous or granulomatous tubercles, adhesions, tubal blockage), hysteroscopy (pale, shrunken cavity with adhesions) and HSG (bilateral cornual block, tobacco-pouch appearance, calcified tube/ovary, rigid pipe appearance of tube, multiple beaded appearance of tube).

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 persistent Tubo-ovarian mass after ATD, persistence of menorrhagia or pelvic pain after ATD, tubo ovarial 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.

Women presenting with Subfertility are best treated by Artificial Reproductive Techniques (ART).

Prof (Dr) Picklu Chaudhuri, Associate Editor
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Review Article: Obstetrics

Viral Infections of the Placenta and its Association with Adverse Pregnancy Outcome

Dr. Raut Shrish Vijaykumar

Abstract

Adverse pregnancy outcomes can lead to severe maternal or infant morbidity and are far more frequent in the developing world. Placentation is a stepwise process of differentiation of the trophoblasts. The placenta, being a dynamic organ, goes through structural and functional changes throughout pregnancy. It is hypothesized that trophoblast cells are susceptible to viral infection and susceptibility to these infections is dependent on differentiation of trophoblast, gestational age at which infection occurs and trophoblast phenotype.

The review is aimed to gather the evidence in support of hypothesis that trophoblastic infections especially viral; cause trophoblastic dysfunction at cellular level and hence placental dysfunction at organ level leading to adverse pregnancy or reproductive outcome/s, to find out viruses which were considered to be low or no pathogenic to placenta and to study pathological mechanisms involved in infection resulting into adverse pregnancy outcome.

It is concluded that there is evidence linking placental infection by viruses like Adenovirus, AAV-2, Coxsackie B, Parvovirus B19 and HPV could be associated with adverse reproductive outcome. It is implicated that trophoblast cells are susceptible to viral infection through the expression of viral receptors. Immunological or inflammatory response mounted by placenta and / or by mother towards viral trophoblastic infection might also be playing a role.

More case control studies using virus specific molecular markers are required to be done to strengthen this hypothesis. It is also important to establish this association to overcome challenges in diagnosis and prevention of these conditions and prediction of its outcome.

Keywords: Placenta, Viral infections, adverse pregnancy outcome, Trophoblastic infection, adverse reproductive outcome

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Introduction

Pregnancy is time period between events of conception to the delivery of products of conception while pregnancy outcome is the result of conception and ensuing pregnancy e.g. birth weight, spontaneous abortion, congenital malformations, lower birth weight, preterm delivery or stillbirth. Even if both the mother and infant survive, pregnancy complications or problems at delivery or during the neonatal period can lead to severe maternal or infant morbidity and should also be addressed while considering pregnancy outcome.[1]

The term adverse pregnancy outcome itself covers diverse group of conditions. Maternal adverse pregnancy outcome includes conditions such as Hypertension in pregnancy except chronic hypertension, established Preterm labour and delivery, Preterm rupture of membranes and first or second trimester miscarriages. While fetal adverse pregnancy outcome included are intrauterine Fetal Growth Restriction (FGR) and Intra-Uterine Fetal Demise (IUFD). The etiology of these could be multifactorial.

Aim and objectives

- To identify viruses which are not implicated previously in pathogenesis of adverse pregnancy outcome or which were considered to be low or no pathogenic.
- To study pathological mechanisms involved in the viral infection trophoblast resulting into adverse pregnancy outcome.

Materials and Methods

Articles were searched from different databases with key words like 'Adverse Pregnancy outcome', 'Adverse Reproductive outcome', 'Viral Placental Infection', 'Viral trophoblastic infection'. Articles implicating viruses in Preterm labor or birth, Pregnancy Induced Hypertension, Recurrent abortions and Intrauterine Fetal Demise were studied.

Placental Development: Physiology of placentation.

The placenta being dynamic organ its structure and functions change throughout pregnancy. Placentation is a stepwise process that characterized by differentiation of the cytotrophoblasts. Two pathways give rise to the differentiated cytotrophoblast cells. In one pathway that gives rise to floating villi, where they are in direct contact with maternal blood. This trophoblast population is specially adapted for transporting a wide variety of substances to and from the embryo or fetus.

In another pathway that gives rise to anchoring villi, invade the endometrium and the one third of the myometrium (interstitial invasion). They also breach the portions of maternal arterioles that span these regions (endovascular invasion) which later completely replaces the endothelial lining and much of the smooth muscle wall of these vessels forming a hybrid vasculature composed of fetal and maternal cells.[2,3] This leads to modification of endometrial and then myometrial parts of spiral arteries. On the basis of extent of invasion of cytotrophoblast, regions in the spiral vessels could be classified as fully or partially modified or unmodified.[4]

Placental Development: Role receptors in viral infections and abnormal placentation:

The susceptibility of trophoblast cells to infection by adenovirus and herpes simplex virus was found to be decreased when trophoblast cells get terminally differentiated into syncytiotrophoblast. This is due to reduced expression of viral receptors. It was also observed that undifferentiated, extravillous trophoblast cells, which are susceptible to adenovirus infection, underwent pathologic changes (i.e. apoptosis) when infected by adenovirus in the presence of decidual lymphocytes which were used to simulate the maternal immune response to viral infection.[5]

Tall Like Receptors TLRs are the family of innate immune receptors that have role in the recognition of pathogen-associated molecular patterns. Some of these receptors may also function as viral receptors mediating viral recognition and entry into the trophoblast.[6]

The pathological significance of placental adenovirus infection that is placental expression of the Coxsackievirus and Adenovirus Receptor (CAR) varied with gestational age and trophoblast phenotype. The CAR was continuously expressed in invasive or extravillous trophoblast cells but not in villous trophoblast cells. It was postulated that the villous syncytiotrophoblast, which does not express CAR and is resistant to adenovirus infection, limits

the transplacental transmission of viral pathogens, including adenovirus. Conversely, extravillous trophoblast cells underwent apoptosis when infected by adenovirus in the presence of decidual lymphocytes. Thus, adenovirus infection and/or the maternal immune response to adenovirus infection induced the death of placental cell types that expressed CAR.[6]

One of the review articles studying viral infection of the trophoblast to placental dysfunction; states that 'there is fragmentary evidence suggesting viral infections might have played a role in abnormal implantation and placentation. This is causing placental dysfunction which leads to complications including spontaneous miscarriage, preeclampsia, fetal growth restriction and preterm birth'. It was concluded that there is evidence linking placental infection by viruses, including viruses thought to be non-pathogenic or to have low pathogenicity, to indicate that this effect contributes to poor pregnancy outcome.[7]

It was demonstrated that the villous syncytiotrophoblast is resistant to Herpes Simplex Virus (HSV) entry. The study was conducted to test the hypothesis that the villous syncytiotrophoblast prevents transplacental transmission of HSV secondary to decreased expression of HSV entry mediators (HveA, HveB, and HveC). Also the ability of HSV to infect extravillous trophoblast cells and the expression of HSV receptors in these cells were investigated using fluorescence-activated cell sorting (FACS) analyses. Immunostaining is done to demonstrate HveA, HveB and HveC. They were not expressed in third-trimester villous trophoblast cells. Conversely, FACS analysis and immunostaining demonstrated that extravillous trophoblast cells expressed HveA, HveB and HveC and these cells were efficiently infected by HSV vectors. Infection of extravillous trophoblast cells by HSV-1 was not reduced when the cells were pretreated with an antibody against HveA but was partially reduced when the cells were pretreated with antibodies directed against HveB and HveC. Thus, the decreased expression of herpesvirus entry mediators in villous syncytiotrophoblast prevents placental villous infection, thereby limiting maternal-fetal transmission of HSV.[8]

Based on these findings, it is hypothesized that trophoblast cells are susceptible to viral infection through the expression of viral receptors and susceptibility to these infections is dependent on differentiation of trophoblast, gestational age at which infection occurs and trophoblast phenotype.

It is also speculated that viral infection of extra-villous trophoblast cells and / or maternal immune response to it may negatively impact the process of placental invasion or placentation and predisposes the mother and fetus to adverse pregnancy outcomes that result from placental dysfunction.

Mechanism of Pathogenicity: Viral invasion theory and maternal immune response theory.

The molecular mechanisms and pathologic significance of placental viral infections were poorly understood previously. It was found that, there is evidence of the placenta playing an integral role in the vertical transmission of viruses, such as cytomegalovirus and human immunodeficiency virus, from the mother to the fetus. Although the consequences of congenital viral infection (i.e. fetal anomalies, intrauterine fetal death, and persistent postnatal infection) may be devastating, very little is known about the passage of viruses across the placenta and the pathologic consequences of placental viral infection. It was postulated that the syncytiotrophoblast is relatively resistant to viral infection. Intrauterine invasion by viruses can be associated with maternal symptoms of infection or can be completely silent. The evidence of infection may be as dramatic as obvious fetal malformation or fetal death or it may be as subtle as nascent intrauterine Fetal Growth Restriction (FGR), mildly inappropriate calcification of fetal organs, placenta, cord, and membranes, and failure to adequately develop fetal fat reserves leading to low birth weight. Rubella, cytomegalovirus (CMV), herpes simplex virus (HSV), and human immunodeficiency virus (HIV), for example, are viruses capable of gaining access to the amniotic cavity and producing fetal infection, even when amniotic membranes are intact.[2]

Epidemiological studies have established the association between viral infections and preterm labor and fetal congenital anomalies. Although some viral infections during pregnancy may be asymptomatic, most of the preterm deliveries are associated with histological evidence of inflammation of the placenta, termed as acute chorioamnionitis or chronic chorioamnionitis. Despite the high incidence

of acute chorioamnionitis, only a fraction of fetuses have demonstrable infection. This shwos the unique ability of the placenta to act as a potent barrier with an immune-regulatory function that protects the fetus from maternal systemic infection.[9]

The Human Papilloma Virus (HPV) was supposed to reduce trophoblastic cell invasion and its infection is associated with adverse reproductive outcomes attributed to placental dysfunction. An apoptosis and invasion assays were conducted to study the effect of HPV using extravillous trophoblast (HTR-8/SVneo) cells. Invasion of transfected cells through extracellular matrices was 25–58% lower than that of the controls. Potential mechanisms by which viral infections may induce failed invasion and placental dysfunction, including altered expression of cell adhesion molecules, matrix metalloproteinases, proinflammatory cytokines and major histocompatibility antigens, need to be explored.[10]

The experiments were conducted using Murine animal model to evaluate the consequences of a viral infection which were characterized by lack of fetal transmission of virus. The animal model described in this work showed that viral infection of the placenta can elicit a fetal inflammatory response that, in turn, can cause organ damage and potentially cause developmental deficiencies. Furthermore, it was demonstrated that viral infection of the placenta may sensitize the pregnant mother to bacterial products and promote Preterm labor. Analysis of the fetuses revealed that viral infection of the mother has a transient effect on development. A delay was observed in the process of differentiation of the eye, tails, and limbs also. Despite the absence of viruses in the fetuses, severe pathological changes in the fetal tissues of infected mothers were noted.[9]

It is to be taken into consideration the fact that during pregnancy it is not only the maternal immune system responding, but also the fetal/placental unit. Interestingly, a significant increase in the levels of fetal proinflammatory cytokines including high levels of IFN-γ and TNF-α was observed. The presence of these two cytokines may explain some of the morphological changes observed in these fetuses. Collectively, these data have suggested that although there is no demonstrable fetal viral infection, the presence of an active inflammatory response in the placenta and decidua can have a direct effect on fetal development. When interaction between trophoblast & viruses was studied it was observed that there was mild increase in modulatory cytokines, such as IL-6, IL-1β and the immune suppressor vascular endothelial growth factor (VEGF). This data suggest that even in the absence of placental passage of the virus, the fetus could be adversely affected by an inflammatory response mounted in response to viral invasion of the placenta. Furthermore, it was demonstrated that a viral infection in early pregnancy sensitizes the pregnant mother to the effects of bacterial products later on in gestation, and specifically, to premature labor. These findings have suggested that exposure to early viral infections might program the immune response of mother and fetus. Such observations have important consequences for understanding the potential risk of viral infections during pregnancy and the importance of adequate surveillance to prevent maternal mortality and subclinical fetal injury, leading to long-term consequences.[9]

Spontaneous abortions:

A study was conducted to confirm whether genital and fetal tissues might be acting as targets for Adeno-Associated Virus (AAV) infection in humans. The earlier animal study demonstrated that the infection with the AAV induces early abortions in pregnant mice. In the human studies, large amounts of viral DNA were detected by southern blot than PCR analysis of fetal tissues obtained after first trimester spontaneous abortions. In situ hybridization revealed that AAV-DNA were restricted to the villous material of placenta predominantly syncytiotrophoblast layer but not to deciduas. Also presence of AAV specific proteins were detected in trophoblast cells by immunofluroscence. Thus AAV infects uterine mucosa possibly persistently and it can replicate in trophoblast cells. Furthermore serological analysis revealed IgM type antibodies to AAV-2 in one third of patients with early miscarriage. This indicates reactivation or re-infection with AAV might be occurring as a consequence of hormone induced mucosal changes or physiological T cell immune suppression during pregnancy. Thus ability of AAV to induce differentiation and to interfere with the development may disturb the differentiation of trophoblast cells and may trigger an arrested development of placenta.[11]

Preterm labor

Although the rate of survival for preterm infants is improved, these infants remain at risk of acute and chronic health problems. The current methods for the diagnosis and treatment of preterm labor are based on an inadequate literature, and little is known about how preterm birth can be prevented.[12]

In a study, the placentas from 108 subjects were collected. Cases were defined as women who developed severe pre-eclampsia requiring delivery before 37 weeks' gestation and women who underwent spontaneous preterm delivery before 37 weeks' gestation subsequent to preterm premature rupture of the membranes and/or idiopathic preterm labor. Controls included women who delivered at term with no obstetrical or medical complications. Women with sexually transmitted diseases during the index pregnancy were excluded from the cohort. DNA was extracted from extravillous regions of placentas from all subjects.[10]

Among subjects in the study, HPV DNA was identified in the extravillous region of 26.9% placentas. Approximately 45% of HPV DNA corresponded with low-risk strains (HPV- 6 and 11) and 55% corresponded with high risk strains (HPV-16 and 18). There were no differences in detection of individual HPV types among the three groups (controls, spontaneous preterm delivery and severe preeclampsia). Identification of HPV DNA in extravillous regions of placental samples from cases of severe preeclampsia was not significantly different from that of controls (p = 0.71). However, HPV DNA was detected more frequently in the extravillous trophoblast region of placentas from cases of spontaneous preterm delivery than from controls (p = 0.03). In the subset of women who underwent spontaneous preterm delivery remote from term (34 weeks' gestation), HPV DNA also was detected more frequently than among controls (p = 0.02).[10]

These results indicate that HPV (HPV-16) is able to infect and replicate in invasive trophoblast cells, induce cell death and reduce cell invasion through an extra cellular matrix. These effects of HPV infection may result in failed invasion by extravillous trophoblast cells into the maternal uterine wall, placental dysfunction and adverse pregnancy outcomes especially spontaneous preterm delivery.

Preeclampsia and Hypertensive disorders in pregnancy:

This medical condition in pregnancy with its wide spectrum has remained a significant public health threat in both developed and developing countries contributing to maternal and perinatal morbidity and mortality globally. However, the impact of the disease is felt more severely in developing countries where, medical interventions may be ineffective due to late presentation of cases. The problem is confounded by the continued mystery of the aetiology and the unpredictable nature of the disease. Many challenges exist in the prediction, prevention, and management of preeclampsia.[13]

Adeno Associated Virus-2 (AAV-2) DNA was found more frequently in trophoblast cells from cases of severe preeclampsia than from normal term deliveries (p = 0.002). These results indicate that AAV-2 infection could be the previously unidentified cause of placental dysfunction. It was hypothesized that infection with AAV-2 inhibits trophoblast invasion and is associated with preeclampsia, which is the common obstetric complication resulting from placental dysfunction.[14]

It is well established fact that extravillous or invasive trophoblast cells mediate placental attachment to the uterine wall and are responsible for establishing a high-flow, low-resistance maternal circulation supplying the placenta and fetus. Shallow invasion or failed invasion by extravillous trophoblast cells into the uterine wall reduces placental perfusion, causes placental dysfunction and hence associated adverse obstetric outcomes, including pre-eclampsia and spontaneous preterm delivery.

In the same study mentioned above, two analyses were performed: 1) comparing rates of AAV-2 detection between cases and controls and 2) comparing rates of AAV-2 detection in extravillous and villous trophoblast cells. AAV-2 DNA was detected in trophoblast cells from the basal plate region in 27 out of 67 placentas; and in 19 out of 27 positives, AAV-2 DNA was detected in both villous trophoblast and extravillous trophoblast columns. AAV-2 DNA was detected significantly more frequently among cases of severe preeclampsia requiring delivery before 37 weeks' gestation than among controls (p = 0.002). If we compared rates of detection of AAV-2 DNA in both villous trophoblast and extravillous trophoblast

between cases and controls, the incidence of AAV-2 infection was significantly greater among cases than controls (p = 0.03). Finally, when comparing the subgroup of preeclampsia cases who delivered remote from term (before 34 weeks' gestation) to controls, the incidence of AAV-2 infection remained significantly greater among cases than controls (p= 0.01).[14]

Stillbirth and Neonatal death:

Retrospective analysis was done with the aim to investigate specific role of infections in stillbirth. Significantly high percent were related to the unknown reasons that lead to the IUFD (34.3%). Study addressing the risk factors of the IUFD revealed that odds ratio is highest for fetal malformation 36.34; for preeclampsia 5.15; for infectious pathology10.93; so it holds the third place after the fetal mal-development and preeclampsia.[3]

There are previous indications that transplacental transmission of cytomegalovirus (CMV), parvovirus B19 (PB19) and HSV types 1 and 2 (HSV-1/2) cause fetal infections, which may lead to fetal death.

In a prospective study, the incidence of these viruses in IUFD and their association with fetal death was examined using placenta tissue extracts and placental histopathological findings of 62 fetal deaths and 35 controls. Among the 62 placental tissues of fetal death, 34% were found positive where as among the 35 controls only 2 (6%) were found positive for any one of the viruses. This result is statistically significant (p = 0.0017) along with other results in cases of Spontaneous abortions less than or equal to 20 weeks (p = 0.025) and Stillbirths (p = 0.0012). In conclusion, an association was detected between viral infection and fetal loss, which was more pronounced in the advanced gestational age. Fetal hydrops and chronic villitis were evidently associated with viral DNA detection in cases of intrauterine death.[15]

Another study assessed perinatal mortality in a well-validated population database of fetal deaths (more than 20 weeks gestation) and infant death for infective causes. The data was analyzed by specific viral cause, timing such as late fetal loss, stillbirth, neonatal death and post-neonatal infant death and across time. Of the 989 total infective deaths, 108 were attributable to viral causes (6.5% of late fetal losses, 14.5% of stillbirths, 6.5% of neonatal deaths, and 19.4% of post-neonatal infant deaths). More than one-third (37%) of viral-attributed deaths were before live birth, from parvovirus (63%) or cytomegalovirus (33%). Parvovirus accounted for 26% (28 of 108) of all viral deaths. CMV was associated with a global loss rate of 3.1 and an infant mortality rate of 1.3 per 100,000 live births; 91% of cases were congenital infections. HSV caused death only after live births with infant mortality rate of 1.4. No changes in rates were seen over time. It was identified that there was substantial contribution of viral infections to global fetal and infant losses. More than one-third of these losses occurred before live births.[16]

A prospective study included 60 pregnant women, with previous bad obstetric history and/or some current pregnancy complication such as polyhydramnios, oligohydramnios or intrauterine FGR. Remaining 29 healthy pregnant women with no history of recent pregnancy complications and matched for age, parity, and gestational age were included as controls. In sera of high risk pregnant women; PB19 infection based on the agent specific IgM antibody positivity was found to be 13.6%. None of the 29 healthy pregnant women in the control group were positive for IgM antibody and this difference is statistically significant ($p < 0.001$). Post-delivery adverse outcomes were observed in 36 of the 60 (60.0%) cases which included abortions (1/7), congenital malformations (1/6), and Non-immune hydrops fetalis (NIHF) (3/3) with no association found with stillbirth. The percentage association of IgM antibodies to PB19 was 8.3%. In five cases of oligohydramnios and six cases of FGR no IgM antibodies to PB19 were detected. Cord blood samples in all three cases of NIHF were positive for IgM antibodies to PB19.[17]

Viral agents such as enteroviruses, adenoviruses, varicella zoster virus and rubella have also been implicated in cases of intrauterine still births or fetal death.[14]

Conclusions

- There are reports to suggest that viral infections of the placenta or trophoblastic tissue might be playing an important role in adverse pregnancy outcome. But more case control studies using virus specific molecular diagnostics are required to be done to strengthen this hypothesis. Such studies will be especially helpful in country like

India where these conditions are more common and where prevalence of infection/s due to these viruses is unknown.

- Such studies will also be useful to establish epidemiological triad of Agent – Host – Environment for adverse pregnancy outcome and throw light on its viral etiology.
- It also supports the hypothesis that such viral infection causes abnormal implantation and placentation which leads to placental dysfunction which is further associated with adverse pregnancy outcome.
- Infections with viruses found to be no or low pathogenic such as Adenovirus, AAV-2, Coxsackie B, PB19 and HPV might be involved in pathogenesis of adverse reproductive outcome.
- Immunological or inflammatory response mounted by placenta and / or by mother towards viral trophoblastic infection might also be playing a role in pathological consequences of adverse pregnancy outcome.

Table 1: showing epidemiological studies done with various adverse pregnancy outcomes and their conclusions

Adverse pregnancy outcome studied	Viral etiology tested	Type of study	Conclusions
Spontaneous abortions	AAV-2	Case control	Virus has ability to interfere with the development which may disturb the differentiation of trophoblast cells and may trigger an arrested development of placenta
Preterm labour	HPV	Case control	Virus is able to infect and replicate in invasive trophoblast cells, induce cell death and reduce cell invasion. Failed invasion by extravillous trophoblast cells into the maternal uterine vessel leads to placental dysfunction .
Pre-eclampsia	AAV-2	Case control	Infection with AAV-2 inhibits trophoblast invasion and is associated with preeclampsia
Fetal death and Spontaneous abortions	CMV, PB19 and HSV-1/2	Case control	Association was detected between viral infection and fetal loss, more pronounced in the advanced gestational age.
Perinatal mortality	CMV, PB19 and HSV-1/2	Case control	There was substantial contribution of viral infections to global fetal and infant losses

Table 2: showing laboratory studies done with various viruses and their results in the adverse pregnancy outcome

Virus tested	Samples collected from	Laboratory method used	Interpretation
AAV-2	Female genitalia	PCR and Southern blot AAV-2 Specific DNA sequence	AAV-DNA was restricted to the predominantly to extra villous syncytiotrophoblast but not in deciduas
	Products of conception after spontaneous abortions	Immuno-fluroscence AAV-2 specific protein	AAV infects uterine mucosa possibly persistently and it can replicate in trophoblast cells
	Maternal serum	IgM Antibodies	Reactivation or re-infection with AAV
HPV	Placental tissue after delivery	PCR followed by sequencing PCR products using primers specific for L1 region	HPV DNA was detected more frequently in the extravillous trophoblast region of placentas from cases.
AAV-2	Placental tissue after delivery	PCR	AAV-2 DNA was detected in both villous trophoblast and extravillous trophoblast columns.
CMV, PB19 and HSV-1/2	Placental tissue and its extract	PCR and Histopathology	Placental tissue of stillbirth were found positive for any one of the viruses. Fetal hydrops and chronic villitis were associated with viral DNA detection in cases of intrauterine death.
PB19	Maternal blood and Post delivery placental tissue	PCR for placental tissue and blood. ELIZA for IgM Antibody.	Infection based on the agent specific IgM antibody positivity e 29 healthy pregnant women in the control group were positive for IgM antibody

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Original Article: Obstetrics

Cesarean Scar Ectopic Pregnancy

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Definition

The cesarean scar pregnancy is an infrequent variety of an ectopic pregnancy in which the pregnancy sac is fully or partially implanted within the scar of a previous cesarean section. But scar ectopic pregnancy has also been reported following: hysterotomy, myomectomy, uterine evacuation, previous abnormally adherent placenta, manual removal of placenta, metroplasty, hysteroscopy etc.[1]

Introduction

The scar ectopic pregnancy is an extremely rare complication of pregnancy. But its incidence is rising together with rising incidences in primary and repeat cesarean sections rates. All over the world, the incidence of primary cesarean section averages 18.6% of all births.[2] The ectopic pregnancy accounts for 1%-2% of all pregnancies.Among all ectopic pregnancy, those occurring within a previous cesarean section scar are again extremely rare and account for 0.03%-0.04% of all pregnancies.[3] The first case of a scar ectopic pregnancy was reported in literature in 1978. Up to 2001 barely 19 such cases of scar ectopic pregnancy were reported in the literature. But by 2007, around161 cases had been reported.[4–6] Till date, more than 1000 cases of scar ectopic pregnancies have been reported in literature. The incidence of cesarean scar pregnancy is regularly increasing day by day. The incidence of CS ectopic pregnancy ranges from 1:1800 to 2216 of all pregnancies. The rate being 6.1 % of all ectopic pregnancies. If a lady has cesarean section, she has 0.15 % chance of having a scar ectopic pregnancy. The cesarean scar ectopic pregnancy is commonly diagnosed at the gestational age of 5–12 weeks. The time interval between the last cesarean section and CS ectopic pregnancy is usually 6 months to 12 years.[7]

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Types of Cesarean Scar Pregnancy

There are two varieties of cesarean scar ectopic pregnancies:

- Type 1 (endogenic) – this variety begins in the cesarean section scar and progresses in the myometrium and develops towards the uterine cavity.
- Type 2 (exogenic) this variety begins in cesarean scar and progresses in myometrium anddevelops exophytically towards the uterine serosa. Type 2 cesarean scar ectopic pregnancies have bad prognosis because they might cause spontaneous uterine rupture, massive internalhaemorrhage which againisdifficult to diagnose and hence may land up in the maternal death.

Pathophysiology

There is a possibility that the pregnancy in the scar implants as there is a defect in the scar. The defect may be in the form of microtubular tract which has developed due to poor healing of the previous scar as a result of cesarean section, dilatation and curettage, hysterotomy, myomectomy, abnormal placentation and manual removal of placenta. Yet the scar ectopic pregnancy is not the same as an intrauterine pregnancy with placenta accreta. In

placenta accreta, there is absenceor poor formation of decidua basalis and this causes varying degrees of invasion of the myometrium by trophoblastic tissues. Yet the pregnancy is basically in the uterine cavity. In scar ectopic pregnancy, gestational sac is totally surrounded by the myometrium and fibrotic tissue of the scar and is lying separate from the endometrial cavity.[8]

Recurrence

If a woman has a scar ectopic pregnancy there is 3.2-5% risk of recurrence of cesarean scar pregnancy in her. The risk factors for recurrence: include a lower uterine segment thickness being less than 5 mm, the gestational sac which bulges into the utero-vesical fold, cesarean delivery in a rural community hospital, history of irregular vaginal bleeding and abdominal pain following previous cesarean scar pregnancy. Theoretically, the surgical management reduces the risk of recurrence.[9]

Symptoms

Some patients are asymptomatic at diagnosis. But most of them presents with pelvic pain and vaginal bleeding usually in the first trimester. The best investigation is transvaginal ultrasound, when combined with a trans-abdominal scan gives a comprehensive information. In doubtful cases, magnetic resonance imaging (MRI) will help in either confirming or refuting the diagnosis.[10]

Differential Diagnosis

The differential diagnosis of cesarean scar ectopic pregnancy includes inevitable abortions with a low lying gestational sac or cervical pregnancies. About 13.6% of cesarean scar ectopic pregnancy are confused as either inevitable abortions with a low lying gestational sac or with cervical pregnancies.[11] The early phase of a spontaneous abortions can mimic cesarean scar ectopic pregnancy; however, in aspontaneous abortions, the gestational sac is often irregular and placed within the uterine cavity. The colour Doppler flows are either absent or minimal. If a gentle pressure is applied with the probe at the level of the internal os, it might displace the gestational sac. This is known as 'the sliding sign'. The sliding sign is classically absent in cesarean scar pregnancy and cervical ectopic pregnancy.[12]

The cervical ectopic pregnancy is present in the cervical canal or close to it. There is ballooning of the cervix, with a good colour Doppler flow around the pregnancy. The sliding sign is negative in cervical pregnancy.

Aim of Management

The aim of management is to prevent the massive haemorrhage and other complications of cesarean scar pregnancy. The uterus is preserved under all circumstances for future fertility of the women. This is important for good health and good quality of life of woman.

The treatment for cesarean scar pregnancy depends on the presentation of the case. It can be managed eitherexpectantly, medically or surgically. The patientshave been treated expectantly in rare conditions. Expectant management is usually not recommended except in conditions which are not diagnosed properly or in conditions where the pregnancies are expected to be spontaneously aborting. The medical management may be considered for haemo-dynamically stable patients. The drug of choice is Methotrexate. It acts best when the scar ectopic pregnancies are less than eight weeks, and where hCG is less than 5000 IU/Land without foetal cardiac activity. The methotrexate can be given either intramuscularly as given in other cases of ectopic pregnancies or direct over the pregnancy sac after aspirating the contents of the gestational sac. Non-invasive therapy with systemic methotrexateshould be considered as an option for stable women.[7]

When serum βhCG levels were less than 5000 mIU/ml and myometrium thickness was less than 2 mm, then systemic methotrexate had success rate of 71-80% and only 6% required hysterectomy.[13]

The surgical management includes excision at hysteroscopy or laparoscopy or laparotomy. The other modalities of management includes: uterine artery embolization, vacuum aspiration under ultrasound guidance.The uterine artery embolisation can be used as an alone treatment for cesarean scar pregnancy. The cesarean scar ectopic pregnancies are a rare presentation of an ectopic pregnancy. It is a condition which is difficult to diagnose and for which a management option remains difficult to decide.

There are also combined mode of management for these cases. In patients in whom more than one mode of treatment is used together or within a short interval is called combined mode of management. The uterine artery embolisation and chemo-embolization are the most commonly combined management procedures used.

Definitely UAE reduces the risk of massive bleeding during suction evacuation. The methotrexate will help in reabsorption of any residual chorionic tissue. Normally the surgical evacuation is planned about 24–48 hours after chemo-embolisation.[14]

The surgical management should be planned for women with significant symptoms or for those who don't want medical management. If the pregnancy is more than 8 weeks, beta HCG more than 5000 mIU/ml or if there is presence of cardiac activity then these patients are better managed surgically.

For patients having endogenous Cesarean Scar Pregnancy, surgical evacuation under ultrasound guidance or hysteroscopic evacuation has lesser chance of uterine perforation and other complications. The surgical resection of the cesarean scar ectopic pregnancywith resuturing may be planned for women with exogenous cesarean scar pregnancy with thin myometrium.The laparoscopic resection may be planned over laparotomy if facilities and expertise are available. Various combinations of management are planned for cesarean scar ectopic pregnancy of longer gestation age and in those with failed or incomplete resolution after first treatment.

Conclusion:

The cesarean scar ectopic pregnancy is a dangerous and rare variety of an ectopic pregnancy. Its incidence is rising parallel to rise in the cesarean section rates in recent years. It is necessary to diagnosis the condition early and accurately. So that an effective management can be done rapidly to reduce maternal mortality and mortality.Awareness of this condition is important among the clinicians. Accurate diagnosis and appropriate management of Cesarean Scar Pregnancy may require a multidisciplinary approach to prevent complicationsof this condition and maternal morbidity and mortality.

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Original Article: Obstetrics

A Study to Corroborate Early Onset Pre-Eclampsia with Uterine Artery Notch Depth Index in Pregnant Women

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Abstract

Objective – to corroborate uterine artery notch depth index with development of early onset pre-eclampsia

Method - study was carried out on 100 uncomplicated primigravida women and uterine artery notch depth index was measured at 20-22 weeks of pregnancy.They were later followed up till delivery to look for development of pre-eclampsia and also perinatal outcome—1) development of SGA, 2) NICU admission etc.

Results – Of the 100 patient we examined 7 developed pre-eclampsia of which 4 had early onset disease. A notch was found in 44 patients of which 50% was unilateral and 50% bilateral. Risk of pre-eclampsia was 8.68 times more among patients having a notch.All the patients with early onset pre-eclampsia had a notch in their uterine artery Doppler which was higher than patients with late onset disease. The cut off value of NDI to predict early onset disease was 0.081 and risk of early onset pre-eclampsia was 9 times more in those who had NDI value> 0.081.However no significant association was found between presence of a notch and development of SGA and NICU admission rates.

Conclusion- NDI values measured in between 20-22 weeks of pregnancy can be a useful predictor for development of early onset pre-eclampsia.

Introduction

Pre-eclampsia is a hypertensive disorder of pregnancy with incidence in nulliparous women ranging 3-10%.[1] It accounts for a major share of maternal, fetal as well as neonatal mortality and morbidity. Hence, some way to predict it early and thus prevent its potentially grave complications remains a challenge. It is divided into early onset disease (<34 weeks POG) and late onset disease (>34 weeks POG).[2] It is early onset pre-eclampsia which is associated with greater risk of perinatal morbidity and mortality.[3] During past two decades numerous biophysical and biochemical tests have been proposed for early detection of pre-eclampsia. Uterine artery Doppler velocimetry is a valuable tool for early detection of pre-eclampsia. Resistant to blood flow in uterine arteries can be important and effective method in predicting obstetric vasculopathies. Resistance to blood flows can be measured by presence of diastolic notch as well as standard colour Doppler indices namely Pulsatility index (PI), Resistance index (RI) and systolic : diastolic ratio(S:D).

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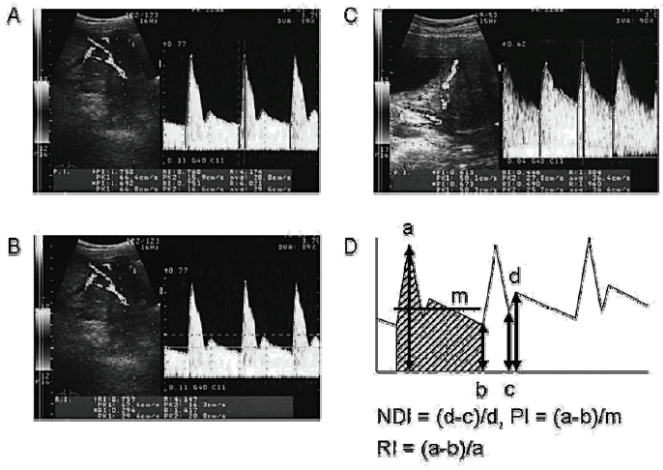

One more concept that is being discussed currently in predicting obstetric vasculopathies is NDI (NOTCH DEPTH INDEX).Uterine artery Notch Depth Index values can be measured by Doppler velocimetry and may be used to detect early onset pre-eclampsia.0kuchi et al developed the NDI to evaluate its association with the risk of pre-eclampsia and SGA infant and to compare its usefulness with that of uterine artery RI and S/D ratio. They found that NDI value in the second trimester is clinically more useful than two other conventional indices.[4] Hence our study aims at corroboration of uterine artery NDI with development of early onset pre-eclampsia and to know the outcome of pregnancies.

Methods

A prospective observational study was conducted in Vivekananda Institute of Medical Sciences, Kolkata among 100 uncomplicated primigravidas. Uterine artery Doppler was performed along with anomaly scan at 20-22 weeks of pregnancy. Uterine artery Doppler velocimetry was performed and when three consecutive waveforms were obtained the NDI was measured and mean NDI of right and left arteries calculated.

The NDI was defined as (d-c)/d in the presence of a notch, or equal to zero in the absence of a notch. Patients were followed up till delivery and their obstetric outcome observed.

Results

Descriptive statistical analyses were performed to calculate the means with corresponding standard deviations (s.d.). Test of proportion was used to find the Standard Normal Deviate (Z) to compare the difference proportions and Chi-square (χ^2) test was performed to find the associations. In the cases where one of the cell frequencies were less than 5 corrected Chi-square (χ^2) was used to find the association between variables. t-test was used to compare the means. Odds ratio (OR) with 95% confidence interval was calculated to find the risk factors. ROC (receiver operating characteristic curve) was used to find the cut-off value. $p<0.05$ was taken to be statistically significant.

Of the 100 patients we examined 44 patients had notch, of which 22 (50%) had unilateral notch and 22 (50%) had bilateral notch. In overall 7% patients developed pre-eclampsia of which 4 (57.1%) were early onset pre-eclampsia and 3 (42.9%) were late onset pre-eclampsia.

Maternal Outcome and NDI:

Table-1: Pre-eclampsia and Notch Depth Index of the patients

Pre-eclampsia	Notch Depth Index		TOTAL
	>0 (Present)	0 (Absent)	
Yes Row % Col %	6 85.7 13.6	1 14.3 1.8	7 100.0 7.0
No Row % Col %	38 40.9 86.4	55 59.1 98.2	93 100.0 93.0
TOTAL Row % Col %	44 44.0 100.0	56 56.0 100.0	100 100.0 100.0

χ^2 =5.31; p=0.021 S-Significant.

Corrected chi square test showed that there was significant association between pre-eclampsia and presence of notch among patients (p=0.021).The risk of pre-eclampsia was 8.68 times more among the patients with notch as compared to the patients without notch and the risk was significant [OR-8.68(1.01,75.07); P=0.021].

Table-2: Type of Pre-eclampsia and Notch Depth Index of the patients

Type of Pre-eclampsia	Notch Depth Index		TOTAL
	>0 (Present)	0 (Absent)	
Early Row % Col %	4 100.0 66.7	0 0.0 0.0	4 100.0 57.1
Late Row % Col %	2 66.7 33.3	1 33.3 100.0	3 100.0 42.9
TOTAL Row % Col %	6 85.7 100.0	1 14.3 100.0	7 100.0 100.0

For all the patients with early onset of Pre-eclampsia (100.0%) NDI was present which was significantly higher than that of the patients with late onset of Pre-eclampsia (66.7%) NDI (Z=3.27;p<0.001).

For all the patients with early onset of pre-eclampsia NDI was present (100.0%). But none of the patient without NDI developed early onset Pre-eclampsia (Z=14.32;p<0.001).

Receiver operating characteristic curve (ROC) was used to calculate cut-off value for both pre-eclampsia overall and early onset pre-eclampsia. For early onset pre-eclampsia the cut-off value of NDI was 0.081 and for overall preeclampsia it was 0.064.

Table-3: Early onset pre-eclampsia and Cut-off value of Notch Depth Index for early onset pre-eclampsia of the patients

Cut-off value of Notch Depth Index for early onset pre-eclampsia	Early Onset pre-eclampsia		TOTAL
	Yes	No	
≥ 0.081 Row % Col %	3 23.1 75.0	10 76.9 25.0	13 100.0 29.5
<0.081 Row % Col %	1 3.2 25.0	30 96.8 75.0	31 100.0 70.5
TOTAL Row % Col %	4 9.1 100.0	40 90.9 100.0	44 100.0 100.0

χ^2 =4.36; p=0.03 S-Significant

Chi-square (χ^2) test showed that there was significant association between Early onset pre-eclampsia and Cut-off value of Notch Depth Index for early onset pre-eclampsia (p=0.03).

However, the risk of Early onset pre-eclampsia was 9.00 times more among the patients with NDI ≥ 0.081 as compared to the patients with NDI <0.081 and the risk was significant [OR-9.00 (1.03, 96.63);p=0.03].

Table-4: Pre-eclampsia and Cut-off value of Notch Depth Index for pre-eclampsia of the patients

Cut-off value of Notch Depth Index for pre-eclampsia	Pre-eclampsia		TOTAL
	Yes	No	
≥ 0.064 Row % Col %	6 19.4 85.7	25 80.6 67.6	31 100.0 70.5
<0.064 Row % Col %	1 7.7 14.3	12 92.3 32.4	13 100.0 29.5
TOTAL Row % Col %	7 15.9 100.0	37 84.1 100.0	44 100.0 100.0

χ^2 =0.93; p=0.33 NS-Not Significant

Chi-square (χ^2) test showed that there was no significant association between Pre-eclampsia and Cut-off value of Notch Depth Index for pre-eclampsia (p=0.33).

However, the risk of Pre-eclampsia was 2.88 times more among the patients with NDI ≥ 0.064 as compared to the patients with NDI <0.064 but the risk was not significant [OR-2.88 (0.31, 26.68);p=0.33].

Table-5: NICU admission and Notch Depth Index of the patients

NICU admission	Notch Depth Index		TOTAL
	>0	0	
Yes Row % Col %	4 66.7 9.1	2 33.3 3.6	6 100.0 6.0
No Row % Col %	40 42.6 90.9	54 57.4 96.4	94 100.0 94.0
TOTAL Row % Col %	44 44.0 100.0	56 56.0 100.0	100 100.0 100.0

χ^2 =1.33; p=0.24 NS-Not Significant

Chi-square (χ^2) test showed that there was no significant association between NICU admission and NDI of the patients (p=0.24).

However, the risk of NICU admission was 2.70 times more among the patients with NDI as compared to the patients without NDI but the risk was not significant [OR-2.70 (0.47, 15.47);p=0.24

Table-6: SGA and Notch Depth Index of the patients

SGA	Notch Depth Index		TOTAL
	>0	0	
Yes Row % Col %	3 50.0 6.8	3 50.0 5.4	6 100.0 6.0
No Row % Col %	41 43.6 93.2	53 56.4 94.6	94 100.0 94.0
TOTAL Row % Col %	44 44.0 100.0	56 56.0 100.0	100 100.0 100.0

χ^2 =0.09; p=0.76 NS-Not Significant

Chi-square (χ^2) test showed that there was no significant association between IUGR and NDI of the patients (p=0.76).

However, the risk of SGA was 1.29 times more among the patients with notch as compared to the patients without notch but the risk was not significant [OR-1.29 (0.24, 6.74);p=0.76].

Discussion And Conclusion

Of the 100 uncomplicated primigravidas 44 had a notch of which 50% was unilateral and 50% was bilateral. Total 7 patients developed pre-eclampsia of which 4 (57.1%) were early onset pre-eclampsia and 3 (42.9%) were late onset disease. The risk of pre-eclampsia was 8.68 times more among patients with notch and the risk was significant (p=0.021).For all the patients with early onset pre-eclampsia (100%) notch was present which was significantly higher than that of the patients with late onset disease (66.7%) and also none of the patients without notch developed early onset pre-eclampsia(Z=14.32: P<0.001).

The cut off value of NDI to predict early onset pre-eclampsia was 0.081.Risk of early onset pre-eclampsia was 9.0 times more among patients with NDI>0.081 and the risk was significant (p=0.03).The sensitivity, specificity and positive predictive value by using this cut off to predict early onset disease was 75%.75% and 23% respectively. There was no significant relationship found between presence of notch and development of SGA babies and also NICU admission rates.

In the study done by Okuchi et al, 9 (3.1%) of the 288 women developed pre-eclampsia and 18 women (6.3%) delivered an SGA infant. The NDI was associated with subsequent onset of pre-eclampsia. The optimal cut off value for the NDI in predicting pre-eclampsia was 0.14, giving a sensitivity, specificity and a positive predictive value (PPV) of 67, 92, and 22%, respectively. The PPV of the NDI was the largest of the three indices evaluated (12% for the RI and 16% for the A/C ratio).[4]

In a study done by R.Becker and R.Vonk to determine whether assessment of depth of notch in Doppler sonography of uterine arteries (DSUA) at 20–23 gestational weeks has the potential to predict the probability of adverse pregnancy outcome (APA) and degree of IUGR.The prevalence of one or several forms of APA increased with increasing depth of the notch from 4.7% (mNI =0) to 46.5% (mNI>0.3).Fetal growth restriction increased with increasing depth of notch from 1.0 MOM or 56th centile (mNI=0) to 0.84 MOM or 21st centile (mNI>0.3).So they came to the conclusion that assessment of depth of notch at 20-23 weeks seems to have the potential to predict the probability of APA and extent of fetal growth restriction.[5]

Our study supports some of the findings of these previous studies and therefore we come to a conclusion that NDI values may have a role in predicting development of early onset pre-eclampsia and further studies are needed for establishing its role.

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Conflict of Interest:

No financial assistance was taken from any funding organization or pharmaceutical company.

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Case Report: Obstetrics

An Unusual Complication in a Case Post LSCS

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Abstract

Background: Acute colonic pseudo-obstruction syndrome, also known as Ogilvie's syndrome is a rare surgical condition that is characterized by acute obstruction and massive dilatation of the colon in the absence of mechanical causes. Ogilvie's syndrome in obstetrics, is mostly associated with the post-operative caesarean section patient. Ogilvie's syndrome may carry a mortality rate as high as 45%[2] and if the signs and symptoms are not rapidly recognized, bowel perforation, fecal peritonitis and death may result. It typically presents 2–12 days post-operatively.

Clinical Characteristics: G2P1L1 37^{+5} weeks elective LSCS done in view of previous LSCS with polyhydramnios with breech in a known case of Ulcerative colitis. Intraop- Uterus dextrorotated, corrected manually. Post op- gradually developed abdominal distension and pain.

Intervention/Diagnosis: Ogilvie's syndrome was diagnosed following an abdominal CT scan which revealed adynamic pseudo-obstruction. It was relieved by simple manoeuvre.

Keywords: Post operative, LSCS, Ogilvie's syndrome

Case Presentation

31 years old G2P1L1 with previous LSCS referred to hospital at 30 weeks with fetal cleft lip & cleft palate in view of NICU facility. Her history included Ulcerative colitis since 8 years on Tab Mesacol 1.2 gm with symptom free period of last 4 years. Her previous cesarean section was 5 years back with uneventful antenatal and postnatal period. She was admitted for elective LSCS at 37 completed weeks in view of moderate to severe polyhydramnios with breech presentation in previous LSCS. Her antenatal profile was normal.

After spinal anaesthesia LSCS was started. Intraoperative findings were 1) Uterus dextrorotated. 2) Left broad ligament vessels anteriorly in incision site. OT table was tilted to left and uterus manually levorotated. This position stabilized by supporting uterus. Membrane ruptured by a nick & gradually liquor drained (~4Lit).

Baby delivered by breech extraction. Shifted to NICU as right cleft lip & palate. Rest of the surgery was uneventful. Patient's vitals were stable postoperatively.

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On 2nd post op day patient mobilized. Abdomen was soft with good bowel sounds. She was tolerating diet. Despite Lactulose patient did not pass stools. Patient slowly developed abdomen distention (>24 hours post op.) & abdominal pain. On examination, vitals were stable, visible abdominal distention was present. Bowel sounds became sluggish.

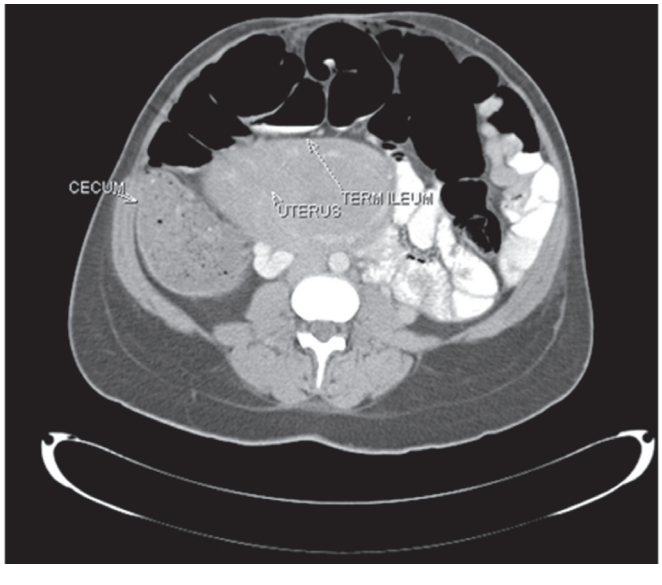
Her family called gastroenterologist (in view of Ulcerative colitis) who advised CBC, Sr. Amylase, X ray abdomen. Reports were normal except USG which was suggestive of sluggish peristalsis. Gaseous distension of the bowels without fluid levels.

Patient was kept nil by mouth; nasogastric tube inserted; there was mild hypokalemia (3.5 mmol/l) so IV fluids and potassium replacement therapy were started. Inj. Perinorm was given.

On 3rd post op day, patient's symptoms persisted. Vitals were stable; abdominal distention persisted with absent bowel sounds. No signs of peritonitis/ obstruction. Urine output was maintained. IV fluids continued. Nasogastric tube aspirate was 50 cc in 6 hours. Differential diagnosis included-

1) Complication of ulcerative colitis 2) Paralytic ileus

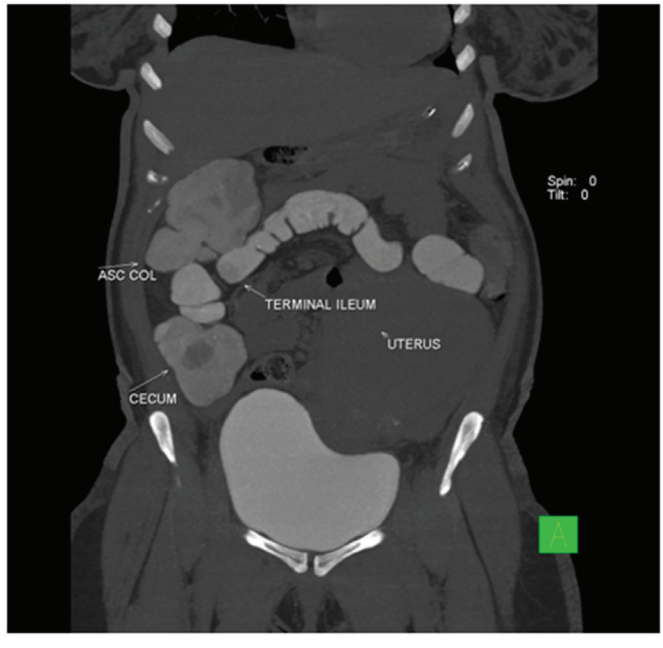
Patient was assessed by gastroenterologist who clinically suspected intestinal obstruction rather than complication of ulcerative colitis and advised CT abdomen. CT was suggestive of bulky uterus in dextrorotated position and pressing the caecum and colon as shown in image below. The condition is known as "Acute colonic adynamic pseudo-obstruction (Ogilvie Syndrome)".



To relieve this pseudo-obstruction caused by bulky dextrorotated uterus, patient was given complete left lateral position.

After 2-3 hours patient started passing flatus. Abdominal girth started decreasing gradually.

Delayed contrast CT after 6 hours of previous contrast showed levorotation of uterus and progressive movement of food particles in colon.



Patient improved symptomatically. Abdominal distension relieved. Ryle's tube removed and graded oral fluids restarted. Patient passed motion.

After 2 more days of hospitalization, patient was discharged in good general health.

An early initiation of supportive treatment, the timely diagnosis of Ogilvie syndrome prevented complications.

Discussion

Ogilvie's syndrome was first described in 1948.[1] and is an acute colonic pseudo-obstruction without a mechanical cause.

Acute colonic pseudo-obstruction is rare and has been reported as isolated case reports or small case series. It is described by a clinical and radiological picture of acute large bowel obstruction without a mechanical cause. It has been reported after pregnancy or Caesarean section, although has also been reported to occur after trauma and severe burns.

The pathophysiology of the condition is still unclear although one explanation is that an imbalance between sympathetic and parasympathetic innervation to the colon results in an overall excess in sympathetic activity.[2]

Ogilvie's syndrome may carry a mortality rate as high as 45%2 and if the signs and symptoms are not rapidly recognised, bowel perforation, fecal peritonitis and death may result.[3]

As the ACPOs have serious complications, timely diagnosis and treatment are critical. Clinical and radiological findings are both needed to confirm the diagnosis of the syndrome.[4]

In ACPO, laboratory findings are nondiagnostic. Some electrolyte imbalances like hyponatremia, hypomagnesemia, and hypokalemia can be seen in ACPO, but they represent a consequence of the pathological condition rather than its etiologic factor. Similarly, leukocytosis can be present, especially with perforation or bowel ischemia. Hypokalemia was present in our case.

Management for uncomplicated patients is initially conservative with limiting oral intake, active mobilization, cessation of opioids, and correction of electrolytes, and underlying comorbidities should be treated.[5]

Intravenous hydration, nasogastric decompression, rectal tube decompression, close clinical monitoring with serial physical examinations, laboratory studies, and abdominal radiological modalities should be done.[6]

The general consensus seems to be that treatment is dictated by caecal diameter. If the caecal diameter is under 10–12 cm, then conservative treatment with intravenous fluids and electrolyte replacement and insertion of a nasogastric tube is recommended. Recently, neostigmine, an acetylcholinesterase inhibitor, given intravenously at a dose of 2 mg over 3–5 min has been shown to be effective if the caecum is not significantly over-distended.[7–9]

However, a caecal diameter that exceeds 10 cm warrants surgical treatment by colonic decompression. If conservative management fail or if bowel perforation or peritonitis develop, then surgery is required, usually laparotomy with bowel resection. In our case, a caecal diameter was below 10 cm and the left lateral position lead to relief of pseudo-obstruction of bowel caused by bulky dextrorotated uterus and was successful.[10]

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A Long Journey with Cervical Tuberculosis

Prof. (Mrs) S.N. Tripathy,[1] Prof. S.N. Tripathy[2]

Introduction

Tuberculosis (TB) has been a major cause of illness and death worldwide for ages and still continues to be so as a major health problem, especially in Asia and Africa The global burden of TB remains enormous. In 2017, there were an estimated 10 million (9 to 11.1 million)new cases of TB and 1.3 million people died from TB, among HIV-negative individuals and 300 000 among people who were HIV-positive. TB is one of the top killers of women, about 500 000 deaths occur every year. 1.7 billion people of the world have latent tuberculosis. India. is one of the highest TB burden countries of the world and it accounts for one fifth of the diseased population. Though it mostly affects the lungs, it can affect all the organs of the body including Genital Organs.[1] (Fig I) WHO adopted End TB strategy to end the global TB epidemic by 2035. zero deaths ,diseases and suffering due to tuberculosis. WHO released the use of Gene Expert for pulmonary tuberculosis in 2011 and for EPTB in 2013. Most of the focus in the past century has been on the successful diagnosis and treatment of pulmonary TB, and tremendous progress has been made in this regard. Hence with collaboration with WHO, the Govt of India formed an Index group for different EPTB including genitourinary Tuberculosis to find out the best form of diagnosis and treatment. The group suggested many investigations like HSG in infertility, FNAC etc, and concluded that the

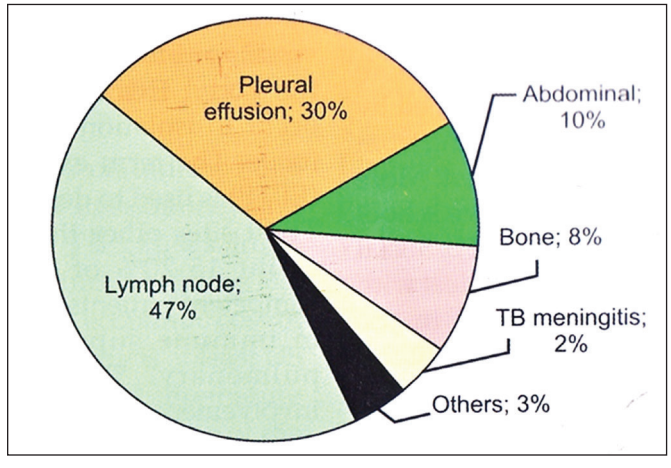

Fig I. Shows the EPTB Incidences

diagnosis of FGTB should be made based on any one of: Laparoscopic appearance typical for FGTB, any gynaecological specimen positive for AFBs on microscopy or positive for Mtb on culture, any gynaecological specimen with findings consistent with FGTB on histopathological examination. Similarly, further evidence is needed on the diagnostic test accuracy of Xpert MTB/RIF and other PCR-based tests. The Govt of India has a Decision and vision of 'TB Free India" by 2025.

In 1744, Morgagni first described a case of genital tuberculosis. Raynaud was the first to report a case of cervical tuberculosis, then Lisfranc in 1842 reported few cases. But later scientists give credit to Virchow for first describing a case of cervical tuberculosis. thinking that the earlier authors might have confused Nabothian follicles for cervical tuberculosis. Robert Koch discovered the tubercle bacilli in 1882.[2]

Pelvic organs are infected from a primary focus, usually the chest, by haematogenous spread. The

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cervix is infected as part of this process, by lymphatic spread or by direct extension. The primary lesion is often healed by the time of presentation. In rare cases, cervical TB may be a primary infection, introduced by a partner with tuberculous epididymitis or other genitourinary disease.

As such tuberculosis of the cervix is a very rare entity It constitutes only 5 % of the genital tract tuberculosis (Tripathy and Tripathy)[3,4,5] varying between 3 to 7%.[6] Though it occurs in the childbearing group, it is also found in the extremes of age. Hardly a few cases are seen by a gynecologist in his or her entire carrier. From 1972 till date we have come across only 41 cases.

Materials and Methods

A total number of 41 cases of histopathologically proved cervical tuberculosis from 1972 to till date (Over 46 years) seen and treated by the authors are taken into the study, All of them are cases of secondary cervical tuberculosis. and each of them can be presented as a case report. The signs, symptoms, diagnostics procedures adopted, treatment given and the treatment outcome is presented. in the study.

Results

The age group varies from 18 to 65 years, but 63 % cases belonged to 26-35 years. Only 3 cases belonged to 55-65 years and one case below 20 years. Majority belonged to low socio economic status, ie 23 cases.

Most of them presented with muco purulent discharge from the vagina, menometrorragia amenorrhea, and post coital bleeding. (Table No I). Four cases presented with post menopausal bleeding.

Table I: Shows symptoms in cervical Tuberculosis

Symptoms	No.	%
Foul smelling vaginal discharge	37	90
Post coital bleeding	30	73
Menometrorragia	24	59
With Infertility	12	30
With Amenorrhea	9	22
Post menopausal bleeding	4	10
Abdominal pain	5	13

On examination, mostly the lesions on the cervix are ulcerative, few are polypoidal, and only four were of schirous type. They exactly look like cancer cervix, bleed on touch, even look like cancer on colposcopy. (Fig II, III) The differentiating point between cancer

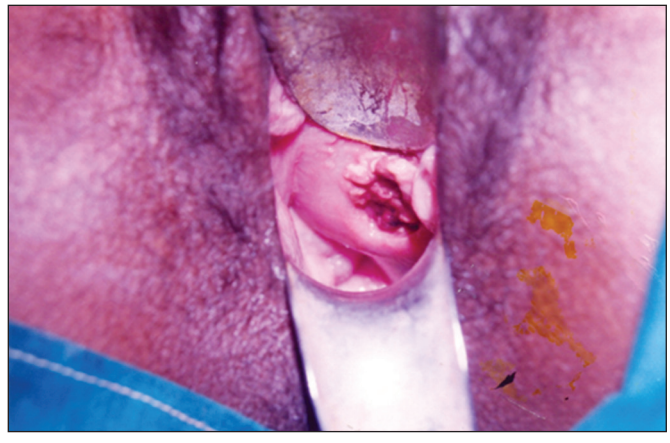

Fig II. Ulcerative Type of Tuberculous Lesion

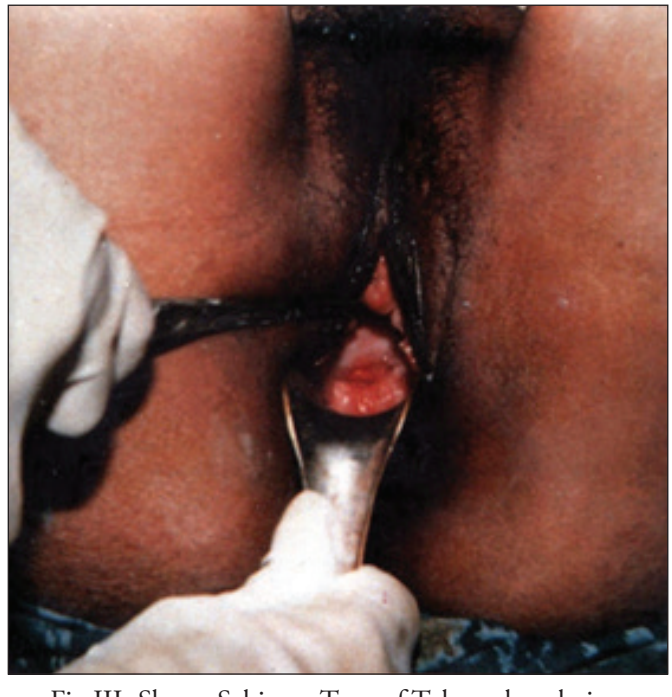

Fig III. Shows Schirous Type of Tuberculous lesion

and tuberculous cervix, is even if the symptoms vary from 2 months to 2 years, there is no indurations. The cervix is fairly movable. (Table No II)

Table II: Shows Types of lesions in cervical Tuberculosis

Types of lesion	N	%
Ulcerative	25	61
Polypoidal	12	20
Schirous	4	10

Pap smear was taken in all cases, but only in 5 cases the smear was positive for tuberculosis, the rest showed inflammatory smears. After a course of antibiotics, biopsy was taken from the cervix in 38 cases. Three cases were subjected to hysterectomy, prior to biopsy, one was a postmenopausal lady with pyometra, due to tuberculous endometritis, two were for PID. AFB

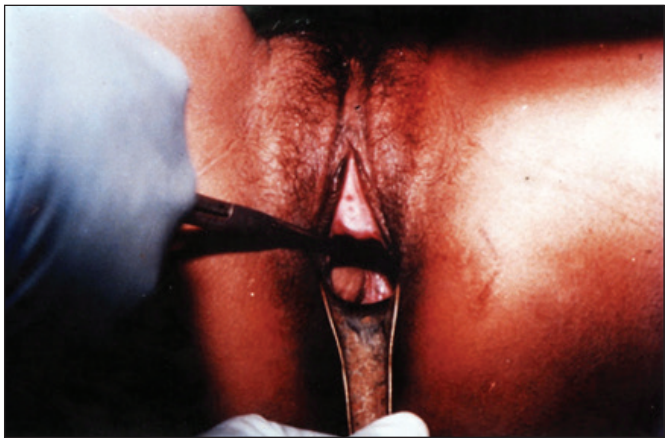

Fig IV. Healed Tuberculous Ulcer

was not detected in a single smear. PCR is not done in any case.

All of them were positive for tuberculosis histopathologically. Only in 5 cases the AFB culture was positive. All were given the short course chemotherapy (2EHRZ+4HR) including the 3 cases who were already had their uterus removed when the diagnosis was made in daily regimen which we advocate. Of course now the WHO has advocated the daily regimen instead of the intermittent regimen. All the ulcers healed completely at the end of the treatment. (Fig IV)

Discussion

Cervical tuberculosis is rare with very few cases reported in literature. The incidence of tubercular cervicitis documented to be 3 to 7.6% of genital tuberculosis, the definite diagnosis of which can be carried out by a cervical biopsy and subsequent histopathology and bacteriology.

Pelvic organs are infected from a primary focus, usually the chest, by haematogenous spread.[7] The cervix is infected as part of this process, by lymphatic spread or by direct extension. In rare cases, Cervical Tuberculosis may be a primary infection,[8,9] introduced by a partner with tuberculous epididymitis or other genitourinary disease. These lesions are extremely rare and usually present as isolated chronic ulcerative lesions of the external genitalia in the absence of TB of the upper urogenital system.

As with other parts of the female genital tract, there are no macroscopic changes in the cervix that are specific for TB. The cervix may appear normal or inflamed, and its condition may resemble invasive carcinoma, both grossly and with the colposcope. The most common type is the ulcerative form, although papillomatous, schirrous and miliary forms may also occur. However Nogales-Ortiz and coworkers stated that a velvety, polypoid appearance is seen frequently,[10] whereas ulceration or destruction of surface epithelium is less common. They also opined that cervical lesions were more common, especially in the endocervix, which was frequently overlooked

Clinically, they simulate a carcinoma, because of the presence of a friable ulcerated growth. This has also been labeled as pseudotumoral tuberculosis of the uterine cervix.[11,12] Cases of tuberculous cervicitis are often clinically diagnosed as carcinoma of the cervix due to the punctation and mosaic pattern observed on colposcopic examination.

Papanicolaou smears have proven to be an immensely important tool in the diagnosis of preneoplastic and neoplastic lesions of the cervix. However, its role in inflammatory conditions is relatively limited especially in diseases that affect the deeper part of the cervical stroma. Cervical tuberculosis is one such inflammatory disease. The cervical smears show inflammatory cells with Langhans type of giant cells, plasma cells, epitheloid cells and ill- to well-formed granulomas in tuberculous cervicitis. Exclusion of tuberculosis or its distinction from a healing non-tuberculous chronic cervical lesion is quite difficult. Histopathological confirmation is needed in such cases.[13] Other differential diagnoses of tuberculosis on Pap smear examination of cervical smears include chronic pelvic inflammation, mycotic infection, enterobiasis, lipid salpingitis, carcinoma, oil granulomas, catgut reaction, and insertion of intrauterine contraceptive device.[14] Pap smears might be normal despite the presence of a cervical or endometrial tuberculous lesion because of inherent problems with Pap smears like faulty technique, non-inclusion of representative areas, lack of proper preservation, etc. Hence, cervical smears are helpful in making diagnosis of genital tuberculosis but do not negate it if smears are normal.

Isolation of the mycobacterium is the gold standard for diagnosis It should be noted that AFB are not always demonstrable in cytological smears. Even with cultures, the results are not optimal. Our results also corroborates the same.

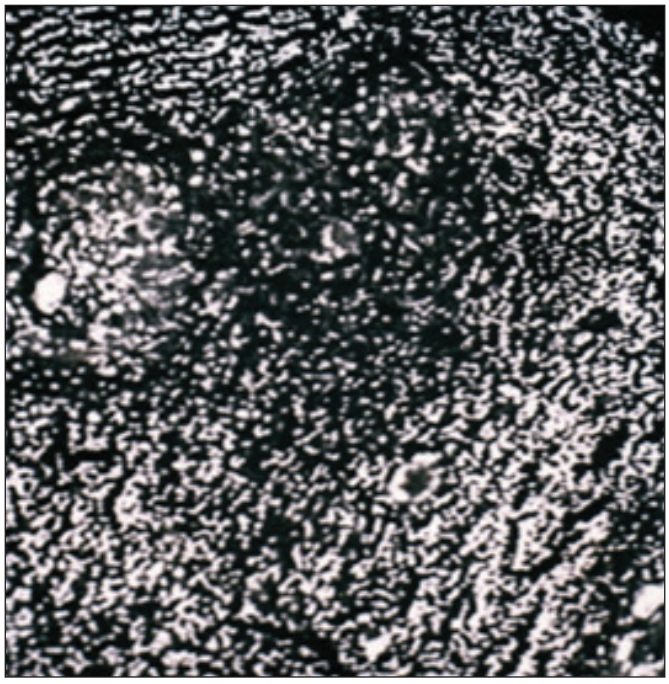

Fig V. Cervical biopsy showing the presence of epitheloid graulomata

The diagnosis of the cervical TB is usually made by histological examination of cervical biopsy specimen. Microscopically, there are caseating granulomata. (Fig V) The differential diagnosis include amoebiasis, schistosomiasis, brucellosis, tularaemia, sarcoidosis, and foreign body reaction.

Ferrara et al diagnosed tuberculosis with the aid of nPCR amplification of mycobacterial DNA fragments on smeared and Papanicolaou-stained cytologic material.[15]

Sonography is another tool to diagnose cervical tuberculosis but is non specific. It can mimic other masses, especially cervical cancer. Though the initial diagnosis of hypertrophic tuberculosis of the uterine cervix presenting with chronic leucorrhea .may be made by endovaginal sonography it has to be confirmed by biopsy.[16–18]

Few case reports are published during last several years, and all have stated that the initial cervical lesion looks like cancer cervix.[19–25] and they all respond to short course chemotherapy.

Therefore, in a young female with suspicious cervix, and absence of dysplastic cells in cytology, tuberculosis should always be considered as a potential differential diagnosis. The presence of epithelioid histiocytes, caseated granulomas and multinucleated giant cells with the typical history of tuberculosis should raise the suspicion of tuberculous cervicitis although culture methods are still the gold standard in the detection of genital tuberculosis.

The incidence of TB has increased recently due to various causes. A high index of suspicion for tuberculosis is justified while dealing with cervical lesions specially from areas where HIV and TB are more prevalent. Chemotherapy is the treatment of choice. We gave (2EHRZ + 4HR) in daily regimen to all cases before the WHO adopted the daily regimen.

The dose depends on the weight of the patient. According to the new guidelines for treatment of extra pulmonary tuberculosis of India, WHO, 2016, in female genital tuberculosis, Intensive phase, EHRZ Rifampicin (R), Ethambutol (E), Pyrizinamide (Z), Isoniazid (H) four drugs for two months followed by continuation phase of four months with three drugs, EHR Clinicians should refer to the current RNTCP guidelines for dosing of ATT drugs. Daily dosing regimens are being introduced now in RNTCP, previously it was thrice weekly regimen. The whole country is now covered, and electronically monitored. Drugs given are, in Fixed Dose combination. (Table III, IV)

Table III: Fixed Dose formulation

Fixed Dose formulation	Each Tablet for 15 kg body weight
Isoniazid (H)	75 mg
Rifampicin (R)	150 mg
Ethambutol (E)	275 mg
Pyrizinamide (Z)	400 mg

Table IV: Recommended doses

Recommended doses	Tablets
<15Kg	1
15-30 Kg	2
30-45 kg	3
45-60g	4
>60 Kg	5

Take Home message

1. Though tuberculosis of cervix is quite a rare disease, a high degree of suspicion leads to the diagnosis.
2. When an unhealthy cervix is mobile and no indurations is there though the duration of symptoms are long standing.

3. The foul smelling vaginal discharge do not disappear after a routine antimicrobials.
4. If plasma cells, Epitheloid cells, giant cells and granuloma is seen in pap smear, investigate the case for cervical tuberculosis.
5. With out doing a biopsy do not treat the case as cancer cervix.
6. Short course Chemotherapy in daily dose Regimen, and fixed dose combinations is the treatment of choice
7. Tuberculosis in other places should be searched for.

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In full-length articles, subject matter should be organized under the following headings, with no subheadings: Introduction; Materials and methods; Results; Discussion; Acknowl edgments; Conflicts of interest; and References.

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The main text of clinical articles should not exceed 2500 words, excluding the first-page information, abstract (no more than 200 words), author contributions, acknowledgments, Conflicts of interest, references (no more than 25), figure legends, and tables and figures. Please include the word count in the cover letter and on the first page of the manuscript.

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Brief communications should be no more than 400 words, excluding the first-page information, synopsis, keywords, author contributions, acknowledgments, conflicts of interest, references, figure legends, and tables and figures. There should be no more than 4 references and no more than 1table or 1figure.

Power calculations, statistics, and reporting of numbers.

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Where appropriate (e.g. for clinical trials), power calculations should be performed as part of the study design, and a statement providing the power of the study should be included in the Materials and Methods. Authors should state how the power calculation was determined, including what type of difference the calculation was powered to detect and on what studies the numbers are based.

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The statistical tests used and the significance level set should be listed in the methods for all studies that employed statistical analysis. Information regarding the statistical software programs used should be included in the methods: for example, "SPSS version 20 (IBM, Armonk, NY, USA)." This information should not be included in the reference list.

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For measures of effect (e.g. relative risks, risk ratios, odds ratios), authors should also report confidence intervals (e.g. 95%) so that the precision of the effect estimate can be assessed.

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Ethics approval

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Sources of funding should be acknowledged by the author(s), along with the names of individuals who do not fulfil the criteria for authorshi p, but who have made a substantial contribution to the manuscript.

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Journal article

[1] Vellacott ID, Cooke EJ, James CE. Nausea and vomiting in early pregnancy. Int J Gynecol Obstet. 1988;27:57-59 .

Book

[2] Speroff L, Glass BH, Kase NG. Clinical Gynecologic Endocrinology and Infertility. Baltimore: Williams and Wilkins; 1982.

Chapter in a book

[3] Disaia PJ, Creasman WT. Invasive Cancer of the Vulva. In: Disaia PJ, Creasman WT, eds. Clinical Gynecologic Oncology. St Louis: C.V. Mosby; 1984:214-219.

Web reference

[4] World Health Organization. WHO Recommended Surveillance Standards, Second Edition [WHO website). 1999. http://www.who.int/csr/resources/publications/surveillance/whocdscsrisr992.pdf.

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