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Opinion Article

Menstrual Blood Seems the Potential Source for Primary Screening of Genital TB (Non-Invasive) Among TB-Burden Country

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Repeated evidence based study makes a consensus that presence of genitourinary infection seems to have a potential impact on infertility [1,2]. It may cause irreversible damage to the reproductive system if early intervention is not done. Infection in either partner can cause reproductive complications that include sperm function, accessory sexual gland dysfunction, and the induction of immunologic responses.

Epidemiological data reveals that Genital tract infections (GTIs) frequently occur in females at reproductive age and associated with increased morbidity related to infertility and other gynecological complications, including urethritis, pelvic inflammatory disease, amniotic fluid infection and preterm deliveries in pregnancy [3,4]. Among them, Pelvic inflammatory disease is the most crucial complication related to infertility as it involves the infection on upper genital tract i.e. endometrium, fallopian tubes, ovaries and pelvic peritoneum, may cause ectopic pregnancy and chronic pelvic pain [5]. Identification of pathogens through non-invasive diagnosis may be a critical determinant for the infection and the spectrum of infections varies as per the geographical and environmental architecture. Majority of western population data reveals that reproductive complications due to infection are dominated by the pathogen like Chlamydia, Nisseriah which are majorly sexually transmitted pathogens. Mycoplasma and Toxoplasma are also considered as potential threats for reproductive complication, particularly in South East Asia (SAS). Recently Mycobacterium tuberculosis (Mtb) and nontuberculous mycobacteriosis are postulated as another etiological agent for Genital TB, particularly for females. Mycobacterium tuberculosis complex (MTBC) is a global burden in the fight against pulmonary tuberculosis (PTB) [6]. Both PTB and extra pulmonary tuberculosis (EPTB) are the leading accelerators for TB-related mortality. The scientific community has already accepted that EPTB is by no means uncommon, particularly in communities where PTB is common [7]. Furthermore, significantly less attention is paid to EPTB than PTB [8,9]. Among the EPTBs, genital TB (GTB) seems to be less of a focus within the scientific community, but irreversible reproductive damage due to this disease has been documented [10]. The estimated incidence of GTB is\1% in developed countries but is 18% in India [11]. The prevalence of GTB is probably largely underestimated because of diagnostic difficulties and its complex clinical manifestations. This is despite the fact it was first identified in 1744 when a 20-year-old woman died of GTB and her post mortem revealed evidence of caseous material in her uterus and fallopian tubes [12].

The genital organs affected by FGTB are fallopian tubes (95-100% cases), uterus (50-60%), ovaries (20-30%), cervix (5-15%), uterine myometrium (2-5%), vulva and vagina (1%). Diagnosis by radiological investigation limits its accuracy as clinical manifestation resembles ovarian cancer, endometrial cancer, Meigs' syndrome, cervical, vaginal and vulvar malignancy. FGTB impacts on various anatomical aberrations that cause infertility through various mechanisms a) FGTB involves Fallopian tubes in almost all cases, usually bilateral, leading to tubal distortion and obstruction with infertility. b) FGTB causes disorder of endometrial receptivity, destruction of endometrium and formation of intrauterine synechiae (Asherman's syndrome). FGTB including latent FGTB has been observed to be an important cause of recurrent implantation failure and recurrent early pregnancy loss due to endometrial hostility through increased

TNF a (tumor necrosis factor a) and interleukin 2 (IL-2) levels. c) FGTB causes ovarian dysfunction through formation of tubo-ovarian inflammatory phlegm on formation and destruction of normal ovarian tissue with poor ovarian reserve.

In spite of rapid advancement of diagnostic facilities, availability of various tests, diagnosis of FGTB remains elusive due to its paucibacillary nature. Clinical history including family history of TB, past history of TB or antituberculous treatment, presence of comorbid conditions, menstrual dysfunction is crucial and a high index of suspicion is needed. Patients with chronic pelvic pain, pelvic inflammatory disease, if usually not responded to routine antibiotic therapy and unexplained infertility should raise suspicion for FGTB. Currently, clinical suspicion aided by intensive investigations are important in the diagnosis of GTB [13]. As an absolute diagnosis from characteristic features in a hysterosalpingogram (HSG) or laparoscopy is not possible, tissue-based culture and histopathological evidence is required [8]. However, these methods are also not sensitive enough to diagnose EPTB with a lower bacterial load [14,15]. The World Health Organization discourages the use of serodiagnostics, such as interferon-c release assays (e.g., QuantiFERON-TB Gold), for active TB diagnosis in the developing world because results are inconsistent and imprecise. This represents an additional barrier to the diagnosis of both EPTB and GTB in the developing world, including India [16]. Routine laboratory processes, including a positive chest X-ray for healed or active PTB, contact history, elevated erythrocyte sedimentation rate (ESR), and positive tuberculin test may be indicative; confirmation requires further investigations [8]. In recent years, polymerase chain reaction (PCR) has become a useful and rapid procedure for the diagnosis of both PTB and EPTB, including GTB [17]. The efficiency of the technique is already proven in PTB [18]. PCR-based GTB diagnosis seems promising but requires premenstrual endometrium aspirates or tissue derived from an invasive procedure, either laparoscopy or dilation and curettage (D&C). Although the PCR-based diagnosis itself is rapid, cost effective and sensitive, significant costs are still involved due to the invasive operative sampling of the endometrium. The invasive sampling process seems to be a crucial barrier to comprehensive clinic-based screening of suspected individuals, so the diagnostic dilemma persists. Given the current diagnostic limitations, studies have postulated to use the menstrual blood as sample source for primary screening. As no gold standard diagnostic methods for GTB yet exist, however the sensitivity and specificity of M-PCR using MB ranges >80% while M-PCR using endometrial tissue was also >80% and for specificity highest for histopathology staining (>90%) however the same limits with sensitivity which is <60%. The LJ culture failed to produce acceptable result as only three samples (<4%) using MB and only seven (9.8%) using endometrial tissue were positive. Infertility due to MTBC is important to consider in a community with a high prevalence of PTB and South East Asia (SAS) is the most vulnerable for TB, at least from epidemiological survey. After the lungs, the genitourinary tract is the most common site for TB infection [19] and recent evidence has shown progression of TB infection from the lungs to the genitourinary region. Clinic-based cost-effective, sensitive, and rapid screening is crucial for the diagnosis of GTB where suspected. Reports have addressed the role of TB in subfertility and infertility A recent report [20] concluded that the prevalence of GTB ranged from 3 to 41% in India and postulated that this range is due to diagnostic dilemma [21]. Currently, the culture-based diagnosis is the gold standard diagnostic approach for PTB, but these methods have severe limitations for EPTB, particularly GTB. It has been anticipated that a significant number of subjects remain undiagnosed because specific non-invasive diagnostic tools are not available. The current invasive procedures, either laparoscopic evidence or D&C for collection of endometrial tissue, seem the most crucial hurdle for GTB diagnosis. Although costly laparoscopic evidence has been reported as being the most sensitive, significant concern surrounds its specificity [8]. PCR using endometrial tissue has been demonstrated as one of the most sensitive diagnostic procedures to detect tubercular involvement in the female genital tract [22]. Our M-PCR-based method using MB provided anon-invasive, rapid diagnostic tool for GTB, an asymptomatic EPTB. It eliminates the invasive procedures required to sample endometrial tissue and their associated pain. The present effort may be crucial as ectopic pregnancy, recurrent miscarriage, tubal abnormality, and unexplained infertility are currently predominant, at least in developing countries such as India. The use of the simple cost-effective method to diagnose GTB in clinic based screening for women of reproductive age seems advantageous as it allows for early chemotherapeutic intervention. Subsequently, it may protect from irreversible damage that often results in failure to conceive. PCR based method using menstrual blood seems may be popular method for community screening for TB elimination strategy which may be confirmed by tissue based PCR along with clinical suspicion [23].

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