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## ABSTRACT

Genital tuberculosis (GTB) in women is one of the common causes of infertility in emerging countries. The important problem in diagnosing and treating GTB is that it often exists in a dormant form without any clinical symptoms. There is a general consensus that GTB not only causes tubal obstruction and dysfunction, but also affects implantation due to ovarian and endometrial involvement. Behavior of the endometrium during the window of implantation in asymptomatic infertile women having dormant GTB is not well understood. The possible molecular association between dormant GTB and endometrial receptivity is, therefore, explored.

Reduced levels of endometrial receptivity markers including  $\alpha\beta3$  integrin, MECA79, E-cadherin, mucin-1 and pinopodes suggest impairment in the receptive status of the endometrium in dormant GTB women. Also, alterations in endometrial thickness, blood flow parameters and VEGF indicate poor angiogenesis during implantation window. Low expression of leukemia inhibitory factor (LIF), LIF receptor and phosphorylated signal transducer and activator of transcription 3 (STAT3) in endometrium of women with dormant GTB indicates compromised LIF-STAT3 signaling pathway which could possibly be responsible for repeated implantation failure.

Metabolomic studies indicate a clear metabolic differentiation in the metabolic profile of endometrium and serum between women with dormant GTB and controls. The significantly altered endometrial tissue and serum metabolites could be largely related to energy metabolism and amino acid biosynthesis. This underlines the metabolic influence of tubercle infection, even in its dormant form. Expression of several serum metabolites followed a similar pattern as that observed in the endometrium of dormant GTB women. The potential of these metabolites as putative diagnostic markers of dormant GTB seems promising.

Since decidualization of stromal cells supports embryo attachment and invasion into the endometrium, the present study also investigates the expression of endometrial receptivity markers, LIF-STAT3 signaling pathway and metabolic profile in *in vitro* decidualized human endometrial stromal cells treated with 65 kDa mycobacterial heat shock protein. Compromised endometrial stromal cells decidualization due to reduced LIF mediated STAT3 signaling and altered metabolism suggests poor implantation potential. Summarizing all these findings, a possible molecular mechanism of implantation failure in women with dormant GTB is hypothesized.

**Keywords:** dormant genital tuberculosis, implantation, endometrial receptivity, decidualization, metabonomics