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Editorial

Does the Thinness of Endometrium Affect the Incidence of Ectopic Pregnancy in Case of Cleavage Stage Embryo Transfer-A Short Communication

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Earlier we have reviewed regarding the anticipation of ectopic pregnancy (EP) in the absence of pelvic inflammatory disease (PID) and further the role of endometrium as a limiting factor in *in vitro* fertilization (IVF) [1,2]. The role of thin endometrium and the relation of spontaneous pregnancy has already been reviewed by certain studies [3,4]. Recently Liu., *et al*. [5], tried to evaluate the effect of endometrial thickness (EMT) on ectopic pregnancy (EP) rate of in frozen embryo transfer (FET) cycles. EP is considered an unwanted result when conducting an *in vitro* fertilization (IVF) cycle, having marked medical, emotional as well as financial effects for the patients. Most studies that have been large and evaluated > 10yr of results in UK as well as USA have demonstrated that that the chances of EP-correlated with IVF has been 1.5 - 2% with it reducing over time [6,7]. This risk seems to be comparable to the United States (US) general population. But the results of individual evaluations differ with EP rates seem to be (2 - 5%) in certain studies - that have emanated mostly from China [8]. Many risk factors for EP are clear like smoking, tubal disease, pelvic adhesions, pelvic inflammatory disease (PID), previous ectopic pregnancy, multiple ET's as well as cleavage stage ET's.

A retrospective cohort study analyzing 17,244 FET cycles which ended in a pregnancy, in a single institution over 8 yr period was done by Liu., *et al* [5]. Following adjustment for known risk factors of EP, they finally summarized that EMT is a marked independent risk factor for EP. All the evaluated cycles presented with an EMT of < 7 mm on the day of progesterone (P) initiation or the day of HCG trigger. There was an inverse relation of EP with EMT. Intriguingly, medicated FET was correlated with risk of EP as compared to modified natural or stimulated cycles.

The biggest strength of the study is the big sample size. Further the advantage was that data was collected from a single centre and hence it reduces variations in the clinical ways as well as laboratory practices along with decreasing operator based differences in ultrasonography (USG) assessments. Further only examining FET cycles also prevents heterogeneity correlated with fresh cycles. But the limitations were that it was a retrospective cohort study. In case of 785 cycles, there was unknown outcome or no record of the EMT. Omitting this missing data might add selection bias.

Liu., *et al*. [5] detailed that they did not possess data on smoking, a known confounder. Further not all confounding factors might have been considered in view of probable unknown factors influencing. EP pathogenesis. They defined thin EMT as < 8 mm in fresh cycles and < 7 mm in FET cycles. Although this is an important clarification that they gave it does not influence the outcome of the posited mode of pathogenesis of EP in this particular study.

Greater EP rate (3.15%) can't help in using it in general for Western populations, who have much EP rate following IVF cycle as discussed (1.5 - 2%). As per the authors >rate of tubal fertility (42.8%) in their population was the explaining factor for EP rate in their

study. The other difference was the embryo selection process that had an objective of freezing high grade cleavage embryos. Embryos possessing suboptimal morphology were cultured further, and frozen if they reached blastocyst stage and possessed good morphology. Maximum embryos got transferred as cleavage embryos (86%). Here lies the separation from maximum programs utilized in the West where exclusively as frozen blastocysts. Though the authors have tried to explain enhanced EP rate with cleavage embryos transfers in their evaluation this separate way of practice might prevent the applicability of their work as far as Western populations are concerned. Further most of the cycles in this study were stimulated FET cycles (47%) as well as had ET of 2 embryos (86%), that is also separate from maximum centres in North America.

Also, Liu., *et al*. [5] Suggested that their observations were contradictory to that of Rombauts., *et al*. [9], on regarding how EMT influences uterine peristalsis. Reversely, following publication of same group along with their explanation matches that of Liu., *et al* [5]. Rombauts., *et al*. [9], have shown that enhanced EMT was correlated with placenta praevia, while thin EMT was correlated with EP. As per them the direction of uterine peristalsis is of great significance with EMT being a marker of fundus-cervix uterine peristalsis [5], there has been a suggestion that women having a previous history of ectopic pregnancy have a 40% recurrence risk of ectopic pregnancy rates following IVF as compared to women with no history of EP [10]. Another mechanism posited for EP is that there are conflicting signals to the embryo from uterine as well as fallopian tube epithelia [11]. It has been seen that thin endometrium demonstrated a separate amount of cytokines as compared to normal thickness endometrium [12].

This is the 2nd biggest retrospective study which suggests that there is a role of EMT that might work as an independent risk variable for EP [5,9]. Thus Liu., *et al*. [5], posited that their outcome might aid in patient counselling. Patients having multiple risk factors for EP like smoking, tubal disease, pelvic adhesions, PID, previous history of ectopic pregnancy, multiple ET's might be a tipping point in decision formation. But with the limitations the questions raised as far as generalizability is concerned, more prospective studies are required before this study can influence the changes in practice [13].

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