

## Utilizing Antibiotics Treatment for Chronic Endometritis Prior to IVF/ICSI Stimulation: Dilemma Needs Resolution Following Report of Enhanced Abortion Rate Following Antibiotics Treatment: A Short Communication

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### Abstract

Earlier we had reviewed comprehensively how there is need for antibiotics therapy for chronic endometritis (CE) prior to IVF/ICSI stimulation in view of better outcomes of IVF/ICSI, with full details of microbiome alterations in endometrium. However recently a report has documented escalated abortion rates subsequent to antibiotics therapy. There the standard diagnostic criteria of  $\geq 5$  plasma cells/HPF was not used instead  $\geq 1$  plasma cells in 10 high power fields (HPF) in study of Duan., *et al.* They found same results on CD 138 Immunohistochemistry. Despite limitations, Cincinelli., *et al.* observed that new caveats have got stimulated regarding diagnostic criteria, cured testing whether biopsy essential or not and advocated greater prospective studies. However their group further conducted a systematic review and meta-analysis over 10 grp studies and observed better clinical, and ongoing pregnancy rate ([CPR], OPR) along with live birth rates (LBR) with antibiotics therapy prior to IVF/ICSI. Further cured CE had better CPR, OPR along with LBR.

**Keywords:** Chronic Endometritis; In Vitro Fertilization; Antibiotics Therapy; Live Birth Rates

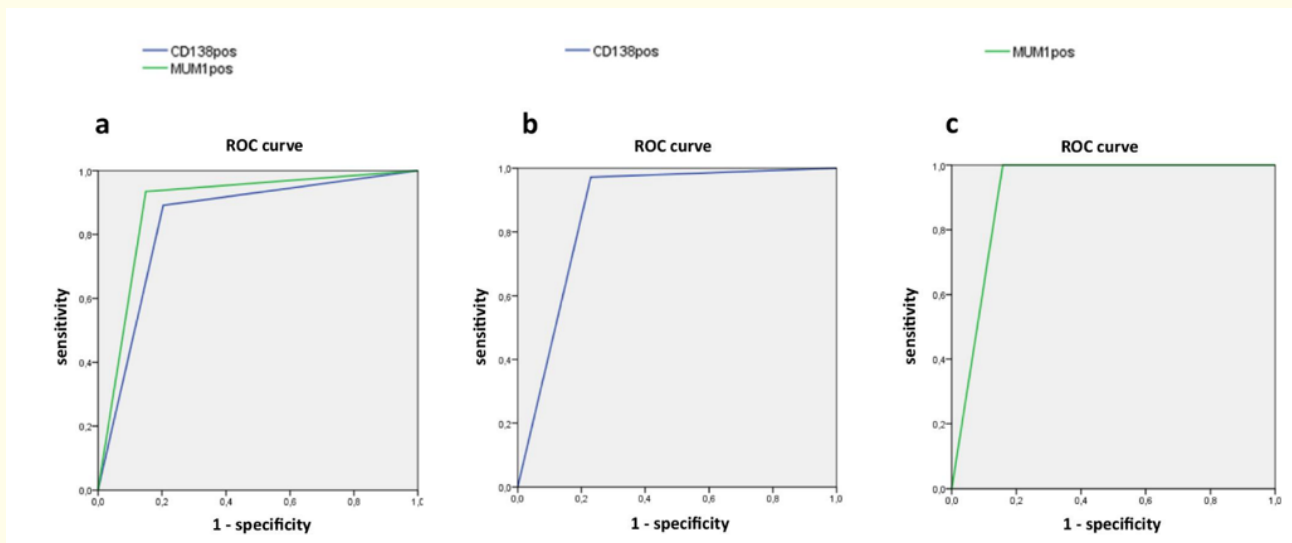
Recently Duan., *et al.* [1], documented the outcomes obtained for last 2 years from their Single centre work regarding *in vitro* fertilization (IVF) in women subsequent to treatment of chronic endometritis (CE) in contrast to negative controls. They conducted a massive prospective study, with the total study cohort (n = 8300) had a hysteroscopy along with endometrial biopsy (EB). Women possessing the evidence of CE at the time of hysteroscopy along with EB were believed to be CE positive. EB was obtained at the time of hysteroscopy that acted as a guide with utilization of a forceps. A 4.07% CE prevalence was disclosed. The treatment of CE was inclusive of initial doxycycline (100 mg bd x 14 days) subsequent to which a 2<sup>nd</sup> dose of levofloxacin lactate (200 mg bd orally/day) along with metronidazole (500 mg bd orally/day) x 14 days if CE continued, thus attaining an accumulated cure rate of 99.1% (of which 93.1 attained cure just subsequent to initial doxycycline course). That CE had undergone resolution was estimated dependent on the total elimination of canonical signs at

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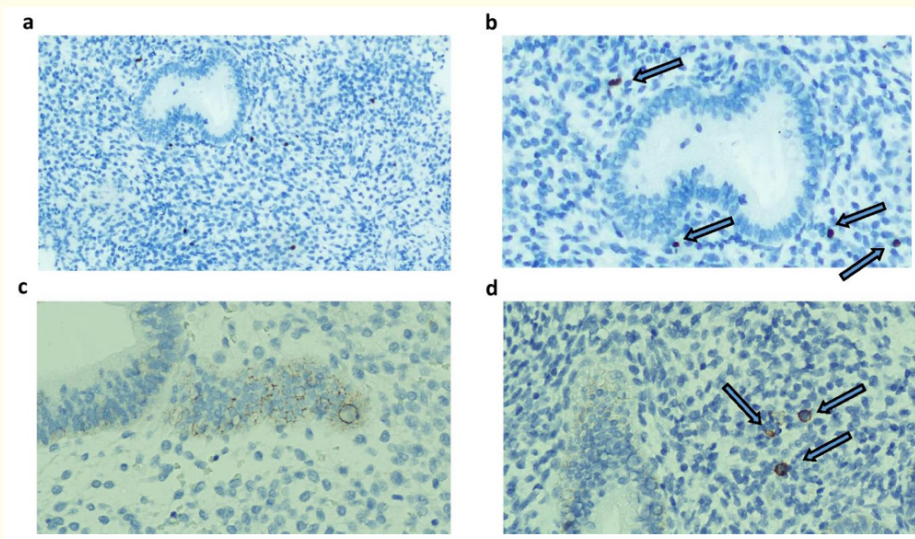
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hysteroscopy without histological corroboration. The primary outcome was to contrast the abortion rates amongst the groups (CE that got cured vis a vis controls). Intriguingly women attaining total cure illustrated greater incidence of abortion rates subsequent to taking care of confounding factors (11.8% vs 9.2%; odds ratio [OR]: 1.49 [1.01 - 2.19], while without adjusting contrasting did not attain statistically significant outcomes. Furthermore, cured CE were correlated with lesser live birth rates (LBR) in contrast to controls (43.9% vis a vis 50.5%; OR adjusted, 0.73 [0.59 - 0.92], while akin clinical pregnancy rates (56.1% vis a vis 60.0%; OR adjusted, 0.83 [0.66 - 1.03]).

Hence this study has evoked newer interest regarding diagnosis in addition to management besides the action of cured CE with regards to IVF results. As far as the prior doubts with regards to CE diagnosis is there, a lack of agreement regarding the least quantities of plasma cells which have to be seen within the endometrial stroma [2]. Cincinelli, *et al.* [2], for the International Working Group for Standardization of Chronic Endometritis Diagnosis showed that multiple myeloma antigen 1 (MUM1) Immunohistochemistry in a multicentre comparative study with CD138 Immunohistochemistry possessed greater dependence in contrast to CD138 Immunohistochemistry in view of generation of CD138 basically by epithelial glandular cells, whereas MUM1 got generated by lymphoid cells like activated B cell along with T-cells (See figure 1 and 2) [3]. Duan, *et al.* [1], utilized  $\geq 1$  plasma cells in 10 high power fields (HPF) in the form of their criteria regarding diagnosis. Nevertheless, other studies observed inimical actions of CE with regards to IVF results in case of women who received no treatment when there was massive plasma cells infiltration (meaning  $\geq 5$  plasma cells/HPF) in contrast to not observed in case of mild plasma cells infiltration ( $\leq 5$  plasma cells/HPF) [4]. Thus, the diagnosis on CE dependent on plasma cell quantities might include variable histological situations having heterogenous effects regarding females fertility [2,4].



**Figure 1:** Courtesy ref no-2-a-c ROC analyses: a diagnostic accuracy of MUM-1 and CD-138 immunohistochemistry for chronic endometritis using histology plus hysteroscopy as a reference standard; b diagnostic accuracy of CD-138 immunohistochemistry for chronic endometritis using a combination of MUM-1 immunohistochemistry, histology and hysteroscopy as a reference standard; c diagnostic accuracy of MUM-1 immunohistochemistry for chronic endometritis using a combination of CD-138 immunohistochemistry, histology and hysteroscopy as a reference standard.



**Figure 2:** Courtesy ref no-2-a-d MUM-1 (a, b) and CD-138 stains (c, d) demonstrate the presence of plasma cells within the endometrial stroma (blue arrows). Note the endometrial glandular/surface reaction to CD-138 antibodies (2c) but not to MUM-1 antibodies (2a).

The other hurdle that has plagued for a long duration is basically related with the ideal gadget used for endometrial sampling. Whereas, utilization of hysteroscopy guide forceps was employed by Duan., *et al.* [1], other groups made use of Novak curette or pipelle [5,6]. Despite, resulting in greater problems to the patients, these devices used aided in obtaining considerably greater depth along with quantities of tissue obtained, thus probably escalated the percentage of retrieval of deep as well as stromal plasma cells that were scattered. Conversely, hysteroscopy is advantageous in aiding the sampling of particular region of endometrium possessing the macroscopic evidence of disease, however the precision of this latter strategy has not been appropriately evaluated. Noticeably, the observation of a prevalence of 4.07% was remarkably lesser in contrast to prior studies conducted on infertile females. Specifically, in Duan., *et al.* [1], study the researchers did not document any lack of consensus amongst hysteroscopic as well as histological diagnosis. That is 338 had the hysteroscopic diagnosis of CE along with CD138 Immunohistochemistry. Whereas, 7962 women illustrated no evidence of CE by utilization of both approaches. This observation contrasted with prior studies that illustrated greater prevalence of CE at the time of hysteroscopy in contrast to Immunohistochemistry [5,6].

The other significant variation of Duan., *et al.* [1], study was the assessment of cure. Despite, their avoidance of a repeat EB on disappearance of any visual evidence of dis subsequent to antibiotics treatment, a prior meta-analysis arrived at the conclusions that treatment of CE escalated the IVF results just when a control EB corroborated that CE had resolved [6]. Hence one cannot negate that there might be continued persistence of plasma cells in what they defined as a cure. Just theoretically once endometrium doesn't assume its original status or incomplete resolution of inflammation/infection itself precludes the chances of implantation alias bad reproductive outcomes inspite of antibiotics treatment of CE.

In the form of a probable reasoning of escalated abortion rates in the CE groups, inimical actions of antibiotics treatment with utilization of doxycycline along with metronidazole might be inimical regarding trophoblastic implantation/ endometrial decidualization has been queried by the researchers. However, acknowledging that both doxycycline along with metronidazole possess shorter half life (8 as well as 22hrs respectively) in addition to long time gap between antibiotics treatment along with embryo transfer (ET) (pointing to a full menstrual cycle for conducting a control EB) the probability of embryotoxic actions of antibiotics is least likely. Conversely, one can posit the changes regarding endometrial microbiome homeostasis subsequent to antibiotics treatment by being inimical to both invading along with residing bacteria. As per residing bacteria, once there is *Lactobacillus* spp dominance ( $\geq 90\%$ ) it has been recently illustrated that it is correlated with positive IVF results as far as prognosis of pregnancies subsequent to IVF is concerned. The precise time of attaining *Lactobacillus* spp dominance subsequent to antibiotics treatment has to be clarified currently. Moreover, utilization of probiotics for rectification of endometrial eubiosis would be an interesting research topic. Nevertheless, antibiotics treatment as well as probiotics was not inclusive of in the study protocol of Duan., *et al.* [1].

Regarding, a statistical point of view another thing that is required is a different detailing over the intergroup variation with regards to abortion rates which was a little greater in CE group (+2.6%; 11.8% vis a vis 9.2%). As admitted by the researchers themselves the outcomes need to be assessed cautiously in view of risk of type II mistake. The full numbers of pregnancies attained in the CE groups was (n = 185) with the surfeit of 9 abortions. Noticeably, with only 1 or 2 lesser abortions, the outcomes would lose their statistical significance. Moreover, the CE group possessed primary infertility (60.4% vis a vis 49%), ovulation conditions (19.5% vis a vis 12.8%) along with male factor infertility (26% vis a vis 23.9%). These all factors might be implicated in the probability of escalation of abortion rates in the CE group. Nevertheless, in view of the study populations was intricate to about 30yrs, the abortion rates in general was agreeable as per the outcomes of National United States assisted reproductive technology Surveillance System (8.2% - 12%) in women < 30yrs of age besides 10 - 13.1% in women of age 30 - 34 subsequent to fresh/frozen embryo transfer). Earlier we had reviewed this topic with emphasis on microbiome, how intrauterine antibiotics might aid in improving prognosis of recurrent implantation failure (RIF). Thus the dilemma persists with more work required in this field with the controversies stimulated [8]. Further extension recently was a systematic review and meta-analysis conducted by Vitagliano A., *et al.* [9], where the assessment of 4145 patients (from 10 studies) were included. Their observation was greater ongoing pregnancy rates (OPR) along with LBR in patients without CE in contrast to robust CE. CE cure escalated both CPR, OPR along with LBR in robust CE. Mild CE did not have much impact, however antibiotics therapy was warranted even with use of CD138 immunohistochemistry alone for diagnosis in these studies. They did recommend antibiotics therapy prior to IVF to improve IVF outcome although warranted more prospective studies regarding mild CE [8]. Subsequently Liu., *et al.* [10], conducted another systematic review and meta-analysis on CE 2145 (from 12 studies) were included. In contrast to controls, CE who received antibiotics therapy did not exhibit any statistically significant variation in OPR/LBR, however abortion rate was lower. Nevertheless, cured CE illustrated greater CPR, OPR along with LBR in contrast to non CE. statistically significant variation, i.e. greater CPR, OPR along with LBR was seen in cured CE in contrast to persistent CE.

## Conclusion

Hence conclusions drawn is that this significant study conducted by Duan., *et al.* [1], might be an eye opener regarding how minimal insight we possess with regards to CE along with what is required regarding having precise criteria for diagnosis, need for control biopsy in the form of assessment of cure. Furthermore, greater insight regarding microbiome homeostasis are important subjects to be tackled to get a clearer picture of need over antibiotics therapy or discard the idea or use with probiotics though they concluded antibiotics therapy is needed, however more prospective studies that are well fashioned are needed to assess any reproductive outcomes of IVF alters subsequent to. Thus, although most studies justify antibiotics therapy for chronic endometritis prior to IVF/ICSI stimulation a dilemma has got created.

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