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Short Communication

Lone Vaginally (V) Delivered Progesterone (P) is Not Subservient to Intramuscular (IM) P Lone or in Combination with (VP in Programmed Frozen Embryo Transfer (FET)/Fresh Embryo Transfer (FET)/Donor Oocyte ET-The Wrong Notion Needs to be Eliminated - A Short Communication

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In the effort for gaining scientific knowledge in reference to clinical medicine, it is not possible to overexpress the significance of the randomized clinical trial (RCT). Practically each cohort study, retrospective or otherwise, concludes with the statement, "there is need for corroboration of outcomes by an appropriately fashioned RCT". Only the RCT fashioning guarantees that patients are allotted to variable therapy regimens randomly. Such strategy usually generates the most authentic conclusions, owing to the result is not impacted by the prejudice of the researcher, a botheration which bewilders plethora of cohort studies. Nevertheless, science is not perfect as well as not full RCTs arrive at the appropriate conclusion. Groups of subjects that are randomly chosen might however not be analogous. For instance, an RCT might not possess the capacity of coming to the conclusion if there is an unacknowledged factor that impacts the results however turns out to be nonuniformly organized in the 2 groups. An RCT can further arrive to the wrong conclusion in case of existence of a systematic mistakes in compliance to the protocol in one of the groups. For instance, in a study where subjects have to self- deliver a particular medication, one group might not actually deliver the dosage prescribed, in addition to thereby enrollment possesses an inimicality of results. i) One instance of an unanticipated, (along with, as per Paulson RJ's view, not right) conclusion obtained from a well-conducted RCT is that the utilization of vaginally delivered progesterone (P) is substandard to intramuscular (IM) delivery incontrived cycles, once no endogenous P is generated. ii) A recent randomized study performed by Devine., *et al*. [1], contrasted IM as well as vaginal P delivery previous to programmed frozen embryo transfer (FET) [1]. Such trial was correlated with a planned preparatory evaluation, whose publication was certain 3 years previous to the ultimately published document [2]. Patients got randomized into three groups: 1) 50 mg/day of IM P only; 2) 200 mg twice a day daily vaginal P only; or 3) a combination of 200 mg twice daily vaginal P plus 50 mg IM P every 3rd day. During preparatory assessment, all 3 groups possessed commensurable rates of positive pregnancy tests subsequent to FET. Nevertheless, one group (that was the just vaginal P group) possessed considerably greater rates of pregnancy elimination (miscarriage, abortion) in contrast to the other 2 groups, with a 33% biochemical pregnancy elimination in addition to a further 22% clinical pregnancy abortion, that resulted in a combined 48% pregnancy elimination. Such pregnancy elimination rate was statistically significantly greater in contrast to the other groups along with resulted in a greater statistically significantly lesser continuing pregnancy rate [2]. Recognized the inimical results combined with a greater magnitude of statistical significance, the researchers omitted enrollment of subjects into the

vaginal P only arm as well as continued the trial with the other 2 groups, whose regimens were inclusive of IM P in addition to, who had occurrence of considerably lesser abortion rates. In the updated ultimate published document, the total pregnancy elimination rate in the just vaginally P arm was updated to 50%, in contrast to 33% elimination in the IM P group along with 26% in the combined P group [1]. Devine., *et al*. [1], labelled the study ''Intramuscular progesterone optimizes live birth from programmed frozen embryo transfer: a randomized clinical trial'' as well as conclusions drawn were that "On the basis of such outcomes, they advocated against progesterone replacement for FET just vaginally alone". Subsequent to their trial, maximum programs that were utilizing vaginal P alone shifted to either IM P or some combination of IM in addition to vaginal P for FET cycles.

Nevertheless, the outcomes of such trial were considerably infrequent as well as not in agreement with earlier trials; such factors, as per Paulson RJ's view [3] in his Editorial, raises query regarding the reliability of the conclusions as drawn by Devine., *et al*. [1].

Once the outcomes of an RCT are seen in the beginning, it is significant to ask if the actual numbers or rates for each group (not imperatively the variations amongst results) are commensurate with earlier studies. If they are not, there needs to be an exposition. Small variations in results from earlier studies can be owing to random disparities, however in case of the large variation, there needs to be a possible exposition for the outcomes being so variable.

One more question that stems is could an existing partiality in earlier cohort studies chosen offer explanation for the same? Is it plausible that every one of earlier studies make analogous errors by not searching for certain specification? Physiologically apparently the vast numbers do not make sense?

The impact of partiality should not be underappreciated. For instance, there is certain debatable issue regarding the results of ovulatory FET cycle in contrast to medicated, or programmed cycles, in which endometrial receptivity gets stimulated by exogenous hormones. Maximum retrospective cohort studies point better obstetric results correlated with ovulatory cycles. Nonetheless, it is pretty plausible that clinicians selected patients who had been ovulating regularly in reference to ovulatory FET in addition to, those who are anovulatory (for instance, PCOS patients) for the medicated FET protocol. Thereby, the variations in results in the 2 regimens might not be in view of the regimens themselves, however instead in lieu of the choosing of variable therapies for the 2 kinds of variable persons. In this condition, a RCT would be considerably aiding in addressing the germanely small variations in results whose meaningfulness is escalated by the large numbers in retrospective cohort studies Nonetheless. in the case of the vaginal vs. IM P trial, it is difficult to fathom the manner the observations of such surprisingly greater rate of 50% miscarriage was not found earlier [4]. The clinical pregnancy rate is probably improved and cycle cancellation rates are probably reduced when starting progestogen the day of or day after donor oocyte retrieval as per Glujovsky., *et al*. [4]. It is tough to imagine a selection prejudice in earlier cohort studies that might have concealed such escalated rate of elimination. If a given group without a grossly distorted endometrial cavity were to experience a 50% elimination rate, maximum clinicians would anticipate that an embryonic factor was possessing a significant part in this infrequently greater elimination rate. Such an embryonic factor might perplex an RCT if one of the chosen groups was somehow, without intention, possessed the susceptibility to aneuploidy. Since the blastocysts that were transferred in the vaginal vs. IM P study were not explored evaluated by preimplantation genetic testing (PGT), this is a possible explanation.

In a natural cycle, the corpus luteum usually generates roughly 25mg of P daily. Therefore, a daily dosage of 25 mg of exogenous P should be sufficient to generate adequate luteinization as well as endometrial receptivity. Patients delivering 200 mg of P vaginally twice daily are taking a daily full dose of 400 mg of P, 16 times the imperative amount of P. Is it plausible that under 6. 25% of the delivered dose got absorbed? This is possible just in case of our acceptance of a considerably greater rate of non adherence with the medication. Plethora of studies have corroborated, that vaginal steroid delivery is correlated with greater absorption in addition to with greater than

anticipated endometrial tissue quantities of P, even with the utilization of particular formulation in this RCT as well [5]. Thereby, 400 mg daily of vaginally delivered P would be anticipated to generate sufficient outcomes.

Additionally, the embryo implantation rate was akin in all 3 of the study groups; just the pregnancy elimination rate was escalated in the just vaginally alone group. If the mode of P supplementation alone were to be involved for such greater rate of miscarriage, the manner indicated by this RCT, then this would delineate the no preexistence of corroboration of certain knowledge that has eluded previous researchers: an empirically stimulated "luteal phase defect" [6].

The outcomes of this well-fashioned RCT should not be ignored. Nonetheless, we have to see that, despite the excellent study fashioning as well as exhaustive data analysis, the data of this study are not commensurate with previous results, nor is there a clear reason for why this would have taken place. There is not a good physiological explanation for normal implantation rates with subsequent 50% pregnancy elimination rate in the just vaginally alone group. We thereby need to conclude that there is, till now, inadequate results to infer that just vaginally alone delivered P is mediocre to IM P in programmed FET cycles.

We need to further conclude that the outcomes of this RCT should be corroborated by further studies. For that to take place, we need to be in agreement that it is not beneath the standard of care therapy in reference to patients with just vaginally P alone along with that it is not unethical to randomize patients to therapy with just vaginally P alone. We might point that the next RCT needs to involve euploid blastocyst transfer to diminish to the least contribution of aneuploidy to the pregnancy elimination rate, in addition to that the patients in the vaginal P arm be particularly educated in the proper delivery of vaginal P [3].

Earlier we had reviewed how for Indian patients where taking vaginally administered progesterone proved to be tough in joint family scenario as emphasized by Prof BN Chakravorty from Kolkata India, nonetheless we did not find any variation in ones delivering progesterone by either routes when just took progesterone vaginally & our stress had been trying to replace vaginally administered progesterone by dydrogesterone orally [7-10]. Here the group of Devine K apparently have been working with such prejudice, of greater abortion with vaginally delivered progesterone. Nevertheless, Paulson RJ stressed on not neglecting these observations, but repeat RCT in PGT assessed FET with either administration route to remove the wrong idea put in against lone vaginally delivered P instead of I/M route which might just add the cost of IVF.

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