

Need for Removal of Fibroids Prior to IVF in Improving Success Rates - A Short Commentary

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Commentary

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Commentary

Uterine fibroids are very common tumors derived from the smooth muscle found in reproductive age women >75% will develop this tumour prior to menopause. Emphasis has been given on when a fibroid is causing hindrance in fertility and warrants removal [1]. Intracavitary fibroids i.e. lying within the entire lumen/project to the cavity and distort its shape are clearly associated with infertility. Such fibroids need removal since besides causing infertility they distort the shape of the uterine cavity, and also lead to menorrhagia, Along with increased incidence of abortion. Since subserosal fibroids lie distant from the uterine cavity, do not affect uterine cavity and typically do not affect IVF results, thus don't need removal. More problematic decision is in the type 3 fibroids, which are quite close to endometrium yet are 100% intramural. Though these ones do not completely distort the cavity once examined by hysteroscopy, but their close presence to the uterine cavity gives a suggestion that they might be impactful.

It has been thought that fibroids exert the side effects on pregnancy by mechanical mechanisms. They distort the endometrium just above the fibroid and change the blood flow. Further they might cause thinning of endometrium just above the fibroid, besides distorting the blood flow. However besides mechanical disruption the bad effects of fibroids are because of their inherent ability to biochemically signal their surrounding environment. Fibroids produce large amounts of

extracellular matrix along with lots of cytokines and growth factors which might have a strong effect on the adjacent tissues. Racknow, et al. first showed a remote effect of fibroids on endometrium [2]. On hysteroscopy endometrial biopsies were got from well defined regions from within uterine cavity, which included areas which were overlying the fibroid, along with areas which appeared unaffected by fibroids. Areas which were far away from the fibroid displayed similar effects on endometrial receptivity (ER), as did areas which were directly over fibroids. There was reduction of HOXA genes, β -3 integrin along with leukemia inhibitory factor (LIF) throughout the entire endometrium, including areas that were visually unaffected by the fibroids. This implies there is a signaling molecule that is produced by the fibroids which reach the endometrium cavity, having obvious implications on IVF success. Thus it is expected that removal of these fibroids is thought to improve local endometrial receptivity immediately present above the fibroids as well as remote from the area of the fibroid. This is similar to the well known inhibitory effects of intramural fibroids on implantation, even if fibroid does not contact entire endometrial cavity. Doherty T 2015 found that the signal to endometrium comes from transforming growth-factor β (TGF- β), which is a diffusible molecule which gets produced in large quantities by the fibroids. TGF β derived from the fibroid impairs bone morphogenetic protein type 1 and type 2 receptors which are essential for endometrial receptivity

[3]. Thus fibroids producing sufficient TGF β , and are in close proximity to the endometrium will allow these signaling molecules to reach the endometrium and have an effect on fertility.

Yan, et al. in a retrospective study examined the effects of type3 fibroids on IVF success. These fibroids are in close proximity or contact the endometrium, although still they are intramural without their presence on hysteroscopy [4]. Though limitations of this study exist in not being a prospective one they still show impacting results. Patients who had type3 fibroids of at least 2cm in size had a significantly lower implantation rates, biochemical pregnancy, clinical pregnancy and lower live birth. Live birth rates increased from 21% to 34% in women who did not have fibroids. Suggestion is given that there is significant impact of fibroid on IVF pregnancy. In women under 40, no other confounding factors were found which could have contributed to these results, which suggest pregnancy rates were directly influenced by fibroids. Even less than 2cm fibroids had an influence on live birth rates. Thus from this study one can conclude that large intramural fibroids in close proximity to endometrial cavity affect IVF success rates by influencing endometrial receptivity along with embryo implantation. Thus one needs to consider removing intramural fibroids if in close proximity to endometrial cavity. Still more trials are needed to see if myomectomy does improve endometrial receptivity.

More TGF β 3 is produced by larger fibroids, with those which are very near uterine cavity allow more TGF β to reach uterine cavity. It is food for thought that if larger fibroids would determine TGF β to reach the cavity would vary by the square of the distance from the cavity ($1/X^2$, where X is the distance of the fibroid from the endometrium, thus both size and distance impacts. Small fibroids distances from the cavity are unlikely to have effects while larger fibroids have greater chance of influencing endometrial receptivity. Since distance would vary as square of the distance, very close fibroids, would profoundly influence the ability of fibroid to influence adjacent endometrium. Small fibroids at distance can be ignored.

Besides the TGF β that gets secreted by fibroids have an effect on the endogenous production of anticoagulants in the normal endometrium which help in regulating normal menstrual flow as shown by Sinclair, et al. [5]. Plasminogen activator inhibitor1, antithrombin3 and thrombomodulin in the endometrium are affected by

TGF β 3. Menorrhagia results because of these changes. Though Yan et al did not report menorrhagia; it is possible that menorrhagia would have predicted the effect of ER. Because both ER and endometrium, anticoagulation both get changed by same signaling molecules it is possible that fibroids which affect bleeding, may also simultaneously affect ER. Still one needs to prove this hypothesis.

Although laparoscopic myomectomy or hysteroscopic removal of fibroids is the surgical removal done conventionally, we have found use of Selective Progesterone receptor modulators like mifepristone available in India or Ulipristal is equally effective in suppressing both kinds of fibroids [6]. Only thing that is required is to check if there is return of HOXA genes, LIF and β 3 Integrin in the endometrium after reduction of these fibroids by this way. In any case need for controlling these fibroids exists to get a good result in IVF.

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