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EC GYNAECOLOGY
Short Communication

Endometriosis Related Infertility-Still Groping in the Dark Despite Multiple Guidelines-No Clear Cut Answers for this Enigmatic Disease-A Short Communication

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Received: July 20, 2020; **Published:** August 05, 2020

I start with this quote from Vercellini., *et al*. that i stole - "I neither know nor i think that i know" from Plato's Socrates, Apology 21d as this is a field where till date we are going in more and more vicious cycle of uncertainties and with spiritual leaders quoting Socrates multiple times in thempi as a person discovered who says he doesn't know anything is miraculous is the true spiritual fellow. Tackling endometriosis remains an enigma and here we further explore the uncertainties of endometriosis therapy a real mysterious disease after having reviewed it umpteen times [1-8].

A systematic review as well as network meta-analysis (NMA) with the aim of contrasting the efficacies of whatever therapies that are available for endometriosis-related infertility, got conducted by Hodgson., *et al* [9]. In contrast to a placebo, GnRH agonists alone as well as laparoscopic surgery alone enhanced the clinical pregnancy rate (PR) to same extent (with odds ratio (OR) 1.68, 95%CI 1.13 - 2.35 respectively). Though the outcomes were depending on minimal data, a hysterosalpingography (HSG) with lipiodol, that is an oil based contrast medium, as well as laparoscopic surgery along with post-operative pentoxyphylline showed further larger efficacy. Not much variation vis a vis placebo was seen regarding the chances of pregnancy for each of the 10 interventions used in the NMA.

They utilized the usual pair wise meta-analysis method, where just 2 intervention were contrasted, by only utilizing the head-head trials and thus contrasting the 2 intervention directly. With the NMA technique a lot of methods used can be contrasted at similar time via combination directly (head-head) as well as indirect proof from randomized controlled trials (RCT). The meaning of indirect proof is to evaluate the relative actions of various therapies which was not got via direct comparison but rather utilizing 1 or greater various common comparators. Simply said, an NMA could be seen in the form of an inconclusive trial, where patients participating could get random used to any of the therapies that were chosen. On the basis of mixed (i.e. direct +indirect) relative effect evaluation, an NMA gives the consent for the hierarchical ranking of the methods that were present for any given problem [10]. A precise primer of NMA for clinicians is present at http://www.ncbi.nim.nih.gov/pmc.articles/PMC5247317/ that was accessed on Oct 19.

It is to be appreciated that Hodgson., *et al*. applied this sophisticated statistical approach in a field that is very complex as well as no definitive therapies. Nevertheless, if the chosen studies is bad or the volume of data present is small, the outcomes of NMA require to get interpreted with care as well as the ranking coming out of it might mislead [10]. In between study both qualitative as well as quantitative heterogeneity seems to be large. There was a non-consistent definition of infertility, with its time period, variable or not given. Other etiologies of infertility, besides endometriosis were very rarely ruled out or excluded. The sample size of various trials was markedly limited, as well as the proof on certain therapies considered was least. Maximum trials were at risk of bias, as well as 6 got published in 80's, hence designing was greater than 30 years back. Certain studies possessed lot of objectives with effect of infertility not the primary aim. Various treatment times were selected for the similar type of medicine (like from 2 - 6 months regarding GnRH agonists as well as 6 - 12 months for pentoxyphylline). In maximum studies PR not live birth rates (LBR) was taken into account. Maximum studies, got carried out

in a single centre, hence limited the generalization of the total outcomes. In view of the lack of knowledge in 40% of studies, the treatment outcome in women in patients with varying severity of endometriosis could not be evaluated. Hodgson., *et al*. themselves admitted that "the majority body of evidence in endometriosis had overall low to very low certainty due to imprecision and concerns on risk of bias'' as well as observations with regards to some interventions need to be interpreted carefully or cautiously [9].

Till now GnRH agonists, as in all present medical therapies utilized for repressing ovarian function, have usually been believed to be not advantageous in women with endometriosis related infertility [11,12]. The proof altered following a single centre large study having 450 patients showed a similar action of a GnRH agonists, laparoscopic surgery alone or combined both interventions [9], with PR varying from 55 - 65%. Nevertheless, conception gets avoided during GnRH agonists therapy, which needs to be taken into account particularly in women with advanced age. Further which are the patients where GnRH agonists therapy is warranted? Ovarian as well deep endometriosis are occasionally picked up on USG, but a laparoscopy is essential for picking up superficial peritoneal lesions, that need immediate therapy. This would enhance the chances of PR just like GnRH agonists would achieve, and thus at this junction, independently of their use. Actually, on the basis of results of Hodgson., *et al*. [9], the actions of laparoscopic surgery as well as post-operative GnRH agonists, are not synergistic.

On thinking of the efficacy of laparoscopic surgery, one has to separate among statistic significance, that is objective clinical significance, that is subjective. On documenting the advantage with regards to crude percentage as well as number to treat (NNT) might promote women's understanding as well as inform their decision. What is the significance of OR 1.63 of conception for lay persons? In practice it means an escalation of the 12 months chances of LBR from a little less than 20% to a little greater than 30%. Nevertheless, this about 10% variation has been shown in randomized controlled trial (RCT) done on minimal to mild, or maximum superficial implants. As right now it is just not possible to pick up this kind of lesions preoperatively, endometriosis will be ultimately diagnosed in just 30 - 50% of women who get a diagnostic laparoscopy for the diagnosis of unexplained infertility [9]. Thus, the advantage of surgery gets diluted since in lots of early stage endometriosis will not get detected. Certain women might not agree for a laparoscopy after the knowledge that roughly 20 procedures are required to get one extra live birth rate (LBR) as compared to expectant management [11,12]. This knowledge will also make health policy makers when trying to calculate the cost benefit ratio for the interventions that are present regarding fertility interventions regarding endometriosis related infertility. These outcomes of NMA do not fit for greater advanced, since trials that evaluate only women with infertility and excluded ovarian endometriomas.

Inspite of certain methodological limitations in the hierarchical ranking utilized for efficacy of therapy, lipiodol-HSG has been documented for quite some time. Nevertheless, the utilization of oil based contrast media was continuous. It was taken over by water soluble contrast media in view of technical, cheap as well as safety issues. The results of lipiodol-HSG is regarding women having endometriosis but fallopian tubes patent. Meaning that lipiodol-HSG appears efficacious in women presenting with minimal-mild superficial peritoneal endometriosis, hence the same population accounted in the RCTs on the advantage of laparoscopic surgery [11,12]. Nevertheless, the NNT of lipiodol-HSG might be markedly less than as compared to laparoscopic surgery. Since the NNT of lipiodol-HSG is 3 in women having previously confirmed peritoneal endometriosis, roughly 6 lipiodol-HSG would be required for getting 1 extra pregnancy in infertile women without an earlier diagnosis of mild-minimal lesions.

As for the opposite, the greater advantage seen for laparoscopic surgery along with pentoxyphylline is a little unanticipated since as per the Cochrane review that includes 3 RCT's [13], 1 clinical pregnancy did not enhance in women with endometriosis utilizing pentoxyphylline as compared to those taking placebo [OR 1.54, 95%CI 0.89 - 2.66].

In view of Hodgson., *et al*. [9] only taking into account natural pregnancy as well as excluding assisted reproductive technology (ART) is a big lack in the NMA. Though ART interventions got included in the systematic review, contrasting with rest of non- ART interventions was not feasible. This evaluation might have been significant and actually the researchers aim to carry out studies on the efficacy of *in vitro* fertilization (IVF) as well as intra uterine insemination (IUI) with other therapies.

The authors correctly recalled the method as well as biometric parameters influencing estimates of efficacy of interventions for endometriosis related infertility are necessary, however treatment related decisions need to be finally individualized. Actually, lot of factors might affect final decision that has included patients age along with what she wants as well as priorities, degree of pain severity as well as various health care services properties of various health care services as well as reimbursement systems. Best thing is the, knowledge on potential advantages of therapies present need to be given separately on regarding women presenting with superficial peritoneal, ovarian or deep infiltrating lesions or for the ones who have had surgery/ART interventions. Already, particularly off the women who do not want IVF, the pelvic pain, besides infertility might tilt the balance in favour of surgery, since this would besides improving the possibility of pregnancy , as well as reduce the pain as well temporarily, hence getting a better quality of life (QOL) during menstruation as well as natural period of trying for conception. Conversely, IVF might be chosen if the risks of surgical damage is escalating in view of the marked anatomy getting markedly compromised as the severity of disease is marked.

As per ESHRE Endometriosis Guidelines Development Group at the time of literature search as well as discussion regarding the availability along with strength of proof, various topics were observed for which enough proof is not there for providing answers for crucial queries [11]. It does not appear that these gaps have been filled till now as lot of years since 2014, Hodgson., *et al*. [9], conclude that there is absence of quality of research in the field of infertility as well as endometriosis, as well as targeted, well designed RCT's are required to be undertaken for further clarity as well as give clear insight on the best management [9]. Till then, informing infertile women with endometriosis of all these unknowns seems key on the time of a clinical decision [14]. Further van der Houwenlee., *et al*. utilize Continuous oral contraceptives versus long-term pituitary desensitization prior to IVF/ICSI in moderate to severe endometriosis for 3 months before IVF/ICSI to see the benefits over 3 months of leupride depot which is cumber some and expensive in severe IVF [15].

Bibliography

1. Kulvinder Kochar Kaur., *et al.* "Editorial-Current controversies and future challenges in Endometriosis therapy". *EC Gynaecology* 1 (2017): 09-13.

2. Kulvinder Kochar Kaur., *et al.* "An Update on Pathophysiology and Medical Management of Endometriosis". *Advances in Reproductive Sciences* 4.2 (2016): 53-73.

3. Kulvinder Kochar Kaur., *et al.* "Meeting the Challenges of Endometriosis Associated Pain-Newer Options for Future and Research Directions". *BAOJ Bioinfo* 1 (2017): 09.

4. Kulvinder Kochar Kaur., *et al.* "An Update on Diagnosis and Management of Adolescent Endometriosis - A Short Communication". *Acta Scientific Paediatrics* 2.5 (2019): 48-50.

5. Kulvinder Kochar Kaur., *et al.* "Dissecting the Reduced Ovarian Reserve Seen with Ovarian Endometriomas with That Caused by Surgical Excision of Ovarian Endometriomas-What Comes First". *Surgical Medicine Open Access Journal* 2.2 (2019).

6. Kulvinder Kochar Kaur., *et al.* "How Can We Optimize the Granulose Cell Function of Oocytes from an Endometriosis Patient to Improve the Reproductive Outcomes-A Short Communication?" *Perception in Reproductive Medicine* 3.4 (2020).

7. Kulvinder Kochar Kaur., *et al.* "An Update on the Various Theories of the Origin of Uterine Adenomyosis –A Systematic Review". *Archives of Urology* 3.1 (2020): 31-45.

8. Kulvinder Kochar Kaur., *et al.* "Developing therapies that prevent progenitor cell migration for preventing the development and further growth of endometriotic lesions-Future Prospects-A Short Communication". *Perception in Reproductive Medicine* 3.5 (2020).

9. HodgsonRM., *et al.* "Interventions for endometriosis- related infertility: A systematic review and network meta-analysis". *Fertility and Sterility* 113.2 (2020): 374-382.

10. Rouse B., *et al.* "Network meta-analysis: an introduction for clinicians". *Internal and Emergency Medicine* 12 (2017): 103-111.

11. Practice Committee of the American Society of Reproductive Medicine. "Endometriosis and infertility: a committee opinion". *Fertility and Sterility* 98 (2012): 591-598.

12. Dunselman GA., *et al.* "ESHRE Guidelines: management of women with Endometriosis". *Human Reproduction* 29 (2014): 400-412.

13. Lu D., *et al.* "Pentoxyphylline for Endometriosis". *The Cochrane Database of Systematic Reviews* 1 (2012): CD007677.

14. Vercellin IP., *et al.* "Which treatments are effective for endometriosis- related infertility?" *Fertility and Sterility* 113.2 (2020): 328-329.

15. Van der Houwenlee., *et al.* "Continuous oral contraceptives versus long-term pituitary desensitization prior to IVF/ICSI in moderate to severe endometriosis: study protocol of a noninferiority randomized controlled trial". *Human Reproduction Open* (2019): 1-8.

Volume 9 Issue 9 September 2020