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Is there Any Justification in Use Oof Expensive *In Vitro* Fertilization (IVF) Add-Ons for Improving Endometrial Receptivity with no Concrete Proof-A Systematic Review

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Abstract

The chances of live birth following in vitro fertilization (IVF) have plateaued despite lot of advances. A lot of extra therapies are available that suggest a lot of effectiveness in enhancing the success of IVF. The idea of this review is to detail whether any benefit is there regarding the add ones utilized with the idea of increasing endometrium receptivity. We included systematic reviews of randomized controlled trials (RCT's) including separate trials. Basically 5 add ones were scrutinized namely Immune therapies comprising of corticosteroids, Intravenous Immunoglobulin (IVIG) Granulocyte-Colony Stimulating Factor (G-CSF), as well as intralipid, Endometrial Scratching; Endometrial Receptivity Array (ERA); Uterine Artery Vasodilation including Platelet rich plasma (PRP) as well as Intrauterine Human Chorionic Gonadotropins (HCG). The results point that no strong proof is there that such add on are efficacious as well as safe. Many of these are expensive and it is better to use that money for any treatment that has been proven by evidence. Need for large RCT's as well as proper safety examination are a must before they get used during routine clinical practice.

Keywords: HIV; Syphils; ASTEL Kit; Dual testing

Introduction

Lot of adjuvant or add on treatments are there for patients planning to get in vitro fertilization (IVF). Though for most of these strong proof of efficacy or safety is lacking them get used a lot [1]. Since no regulations exist with regards to use minimal worldwide data as per their use is not known; still it is believed that 74% of women having IVF performed in UK utilized 1 or ≥1 add-ons in 2018[2]. Many variety of add ones are interventions that are those meant to enhance the follicular response to ovarian stimulation, enhance the culture conditions as well as quality of growing embryos, or prime endometrium as far as impending implantation is concerned.

Although IVF technology has improved gradually with time, pregnancy rates just plateaued with lot of high quality embryos refusing to implant. Lot of IVF cases are confronted with a diagnosis of recurrent implantation failure (RIF), following various repetitive unsuccessful embryo transfers (ET's). In view of this concentration has moved on the part played by endometrium in implantation [3]. Different add-ons have become available in market saying they help in endometrium receptivity as well as enhance the possibility of live birth. Thus here we try to study the proof that is there regarding frequent IVF add-ons regarding improving endometrium receptivity. This topic has earlier been taken up in [4,5].

Methods

We did a PubMed search for most add-ons that are utilized today for IVF to improve success in pregnancy rates as well as live birth rates by improving endometrial receptivity using the MeSH terms like Immune therapies comprising of corticosteroids, Intravenous Immunoglobulin(IVIG) Granulocyte-Colony Stimulating Factor(G-CSF), as well as intralipid, Endometrial Scratching; Endometrial Receptivity Array (ERA); Uterine Artery Vasodilation including PRP as well as Intrauterine Human Chorionic Gonadotrophins (HCG). For every add-on, the present rating given by the UK Human Fertilisation and Embryology Authority (HFEA) was grouped. Green has been assigned if >1 quality RCT has shown the add-ons to be efficacious as well as safe ,amber for those where there is contradictory proof and red if no efficacy as well as safety found[4].The HFEA has rated 11 add ones, and not all add ones reviewed here.

Results

We found a total of 450 articles including all groups, out of which we selected 68 articles for this review. No meta-analysis, was conducted.

Immune Therapies

Usual belief is that the maternal immune system causes damage during early gestation, thus needing suppression [6]. Yet No good quality proof is there to corroborate this, with classical properties of inflammation are not visualised in deciduas at early gestation [7]. The immune cells implicated for implantation failure are the specialized uterine natural killer (NK) cell (uNK). This notion gave the idea that NK cells attack the fetus, resulting in implantation failure as well as pregnancy loss. NK cells that circulate in peripheral blood are actually cytotoxic for virally infected or cancerous cells. Yet uNK both phenotypically as well as functionally are much different from those in blood and come in contact with placental trophoblast cells and not the fetus [8]. Actually in vitro uNK can't kill trophoblasts [9]. Inspite of these observations, a remarkable increase in utilization of assays as well as treatment made to find and correct the apparent immunological changes within the endometrium; these kind of add-ons were utilized in 8% of UK couples getting IVF in 2018 [2]. There are 4 frequently used Immune therapies that are proposed as add-ons to IVF, all have been hypothesized to suppress the inflammatory as well as immune state of the endometrium and thus enhance the chances of implantation as well as pregnancy.

Corticosteroids

Usually Corticosteroids like prednisolone are given for the therapy of inflammatory problems like systemic lupus erythematosus (SLE) as well as rheumatoid arthritis (RA). They are also offered to patients undergoing IVF at time of ET. A Cochrane meta-analysis of 14 studies decided that peri-implantation glucocorticoids gave no additional benefits as far as live birth or pregnancy rates were concerned [10]. These got reaffirmed more recently in other systemic reviews [11,12]. The utilization of Corticosteroids in patients possessing autoantibodies needs more evaluation; enough proof is there to recommend no routine utilization of Corticosteroids for IVF [11]. Moreover the safety of these Corticosteroids for developing fetus has not been examined. Only observational studies documented probable causal correlation among peri-implantation as well as 1st trimester glucocorticoids exposure as well as risk of oral cleft, major con genital anomalies, prematurity as well as low birth weight [13]. Actually US Food and Drug administration (FDA) has given category D rating for prednisolone, in view of adverse drug actions on fetus. Prednisolone being a cheap drug, having cost <$10/IVF cycle [9,14].

Intravenous Immunoglobulin (IVIG)

IVIG constitutes an important treatment modality in various autoimmune as well as inflammatory disorders along with primary immune deficiencies. On systemic immune systems its actions are complicated and the way it might influence the uterine immune system is completely unclear [15]. A recent systematic review had 2 small trials examining the administration of IVIG at the time of ovarian stimulation or near the time of ET and revealed no advantages [11,16]. IVIG has to be used under medical supervision with known side effects like tachycardia, thrombo-embolic complications as well as anaphylactic reactions [17]. The UK Department of Health does not recommend IVIG for IVF-failure [18]. Moreover IVIG is expensive, with a cost of US $2000 to $14,000/ IVF cycle [19].

Granulocyte-Colony Stimulating Factor (G-Csf)

G-CSF is a cytokine that gets liberated by immune cells like macrophages and recombinant human G-CSF is usually used for the therapy of haematological problems like neutropenia. It can be used in the form of intrauterine administration or subcutaneous injection near the time of ET, mostly in women having a thin endometrium or RIF. In IVF its reasoning for use is not known, and it is also costly i.e $100 to $599 [8,20]. Only a Cochrane protocol is there, with this review continuing. Other systematic reviews observed 10 RCT's and documented probable advantage of G-CSF infusion on the chances of achieving clinical pregnancy [11,21]. But lot of clinical trials did not give a clear detail regarding randomization, were heterogeneous and didn't examine live birth rates (LBR), thus proof is not enough to recommend for

or against the utility of G-CSF in clinical practice [5].

Intralipid

An emulsion of soybean oil, egg phospholipids, as well as glycerine is what Intralipid is made of, usually given as iv nutrition for pts not able to tolerate an oral diet. Intralipid Is also believed to manipulate immune function as well as has been seen to decrease the possibility of spontaneous abortion in a mouse model [22]. A systematic review found just a single trial i.e a double-blind RCT that found that intralipid administration to women having increased NK amounts did not increase chemical; pregnancy rates (PR) [11,23]. Cost of this adds on is about US $300 [24]. Although intravenous fat emulsions are usually well tolerated, complications like jaundice as well as hyperthermia have been documented [25]. Moreover severe side effects like immune therapies were thought to have led to a twin pregnancy disturbance at 23 wks., after severe systemic candidiasis formation [26]. Thus there is red rating by the HFEA regarding reproductive immunology testing as well as treatment.

Role of Endometrial Scratching

Endometrial Scratching is a method utilized for disrupting or damaging the endometrium, mostly via the action of a pipelle biopsy, a common gynaecologic procedure carried out for finding possible intrauterine pathologies. This is also done in luteal phase of cycle before IVF [27]. The inflammation occurring as well as stimulation of immune pathways is thought to stimulate the receptivity of endometrium for an implanting embryo and despite various other theories suggested the biological usefulness of Endometrial Scratching has been queried. It is a little difficult to visualize how any advantage can be continued following full functional layer of endometrium is removed and gets redeveloped in between the procedure as well as embryo implantation [28-30]. It was the commonest add on in UK in 2016 [1]. In 2018 it was utilized in 27% of IVF cycles in UK [2]. Roughly 80% of doctors in a survey carried out among New Zealand (NZ), Australia, as well as UK recommended this procedure for their patients, with cost varying between USD$65 -$500[27].

The Cochrane review regarding this is getting updated right now. From the earlier update where 14 randomized controlled trials (RCT's) were utilized, some probable advantages were documented from Endometrial Scratching prior to IVF, with subgroup analysis [31]. Recently conclusions matching these have been documented by a lot of systematic reviews [32]. Greater than 30 trials have got published till date with more on way. Inspite of lot of work, it is still problematic for interpretation, the documented actions of Endometrial Scratching vary from little benefit to marked harm [33]. From a large trial of >1300 women data described no advantages of Endometrial Scratching in women planned for IVF, with subgroup evaluation not isolating any subgroup who might benefit [34]. Although some workers thus say it is better to totally give up Endometrial Scratching others point that some (undefined) subgroups might still benefit via this method [35, 36].

Endometrial biopsy (EB) has a safety profile that is acceptable with few side effects [like vasovagal reaction, infection).But the procedure is a little painful. In the trials that are available, patients complained of pain scores between 3-7 of 10 with the procedure given up secondary to pain in a lot of cases [33,34,37]. Right now HFEA labels this procedure amber.

Role of Endometrial Receptivity Array (ERA)

This is an innovative diagnostic test based on microarray techniques, developed by a commercial group. It needs a correctly timed EB for measurement of the endometrial expression of 248 genes [38]. A prediction model is then used to label the Endometrium as receptive, pre receptive or proliferative. This labelling then aids the women to get a personalized ET, wherein the exact timing of transfer has been tailored for each woman's specific window of implantation.

This ERA has repetitively shown that about 25% women presenting with RIF have > chances of displaced window of implantation. Further, the test used for same women biopsied in multiple cycles will repeatedly give the same outcome [38,39]. But till date, only 1 RCT has been finished, for whom interim as well as preprotocol analysis are present [40,41]. Hence it is not possible to affirm if ERA raises the probability of live birth.

Inspite of lack of strong proof from RCT's in ERA, it is used extensively in IVF centres all over the world.>55,000 ERA tests have been carried out in 60 countries [42]. Analysis of the ERA by external workers is needed to give independent proof of examination of this add on, as pointed by others [43]. Still at the cost of US$800/test a properly powered RCT that enrols >1000 women would need $400,000 USD for recovering ERA cost itself. This ERA test needs an EB, and makes it compulsory to freeze-all cycles and continued cycles in which medication is given to be able to conduct an EB for aiding in ERA biopsy followed by personalized ET. As it is, side effects with endometrial biopsy (EB) as well as squeal of delays as well as cost due to freeze all with recurrent cycles .need to be taken into account. Right now this is not rated by HFEA [44].

Uterine Artery Vasodilation

Vasodilators have an impact on widening of blood vessel lumen and escalate blood flow and get utilized usually for therapy of problems like hypertension as well as erectile dysfunction. Thin endometrium, which is commonly by definition <7 or 8mm.is commonly correlated with decreased chances of pregnancy at the time of an IVF cycle [45]. Thus Vasodilators like sildenafil are advocated to effect relaxation of uterine vasculature, enhancing blood flow to the uterus as well as Endometrium ending in an Endometrium that is thicker along with better receptivity of the Endometrium. If it is effective this therapy would probably be cost effective since cost of sildenafil is about US $20/dose [14]. A current Cochrane review comprised of 15 trials analysing Vasodilators in women undergoing IVF [46]. They documented escalated EMT to be correlated with the utilization of Vasodilators and pointed that they enhance the probability of pregnancy in women having IVF; but, evidence on LBR is not clear since only few trials gave this outcome. Moreover Vasodilators correlated with >side effects like headache as well as tachycardia. Actually sildenafil correlates with various drug reactions like flushing, headache, abnormal vision as well as insomnia [47]. Various other interventions are suggested for escalating EMT, like aspirin as well as PRP.

Role of Platelet rich plasma (PRP)

Autologous PRP is derived from an individual's whole blood, and then centrifuged to remove red blood cells. The remaining plasma has a 5-10 times greater concentration of growth factors as compared to whole blood. These growth factors have been found to promote natural healing responses by researchers from varied specialties including dentistry, urology and gynecology [48,49]. In the field of reproductive medicine PRP has been thought to be an option for making the, Endometrial milieu as well as ovarian reserve [50,51]. An in vitro study pointed that PRP might affect Endometrial regeneration [52].

A recent RCT had 83 women enrolled having a frozen ET(FET) with EMT<7mm. The participants in the study arm had an intrauterine infusion of 0.5 to 1.0 ml of PRP, along with a 2nd PRP infusion given if the EMT did not reach 7mm. The evaluation on intention to treat pointed no significant differences in on-going pregnancies between the 2 arms (33.2%vs 18.2%; p=0.260]. The study was limited having small sample size as well as poor reporting methodology [53]. The only RCT for PRP in RIF included 90women and got published as a conference abstract [54]. In women having a FET there was a significantly > clinical PR (53.3%vs 24.4%; OR3.63; 95% CI, 1.48-8.90, seen in the PRP arm as compared to control group [55].

There are no published RCT's on the role of PRP in improving ovarian response. Limited work is there with case series of poor responders [56-58,59] Natural conceptions as well as LBR was reported after IVF with PRP injection in poor responders [56]. Use of PRP is not approved by the US Food and Drug administration (FDA) and hence off label use is there. Right now use of PRP in reproductive medicine needs to be thought of as experimental.

Recent Guidelines suggest that there is minimal proof to support their utilization [60]. Currently this add-on is not rated by the HFEA.

Intrauterine Human Chorionic Gonadotropins (HCG)

A hormone that is synthesized at the time of pregnancy HCG is thought to control embryo implantation. Usually HCG is commonly used at the time of IVF cycle for triggering final maturation of oocytes, costing about US $40 [14]. Intrauterine Infusion of HCG has been demonstrated to up regulate cytokines which we know have a role in implantation [61]. Injection or instilling HCG into uterine cavity before ET is thus advocated for enhancing the possibility of a successful implantation by making sure that adequate amounts of HCG are there.

A current Cochrane review found 17 RCT's [62]. Saw that lot of heterogeneity among trials and hence were not able to pool the trials in total. But on subgroup evaluation, it seems that of women who have cleavage stage ET, an HCG dose of ≥500IU enhances the probability of clinical pregnancy as well as LBR. Since this observation was seen only in subgroup revaluation, current proof does not support the use of HCG injection routinely. Currently this adds on is not rated by the HFEA.

Quality of Evidence

Out of the 5 add-ons that were evaluated 3 like Endometrial Scratching, Vasodilators, instilling HCG had been analyzed via Cochrane review, that take a Grade of Recommendation, Assessment, Development and Evaluation(GRADE) assessing the Quality of Evidence [63-68]. In all cases this Quality of Evidence differed from very little to moderate Quality and in no case high Quality proof was obtained. The authors related to Cochrane review tried to downplay the proof for risk of bias, inconsistency as well as not precise. Like in an Egyptian study regarding Endometrial Scratching before IVF documented a LBR of 67% following Endometrial Scratching act 28% in the control lot giving an odds ratio of 4.88(95% CI-3.22-7.40) favouring Endometrial Scratching [33]. This huge effect size, with a LBR OF 67% is not likely.

The heterogeneity of study outcomes seen by most of included systematic reviews might be secondary to varying methods among trials or the population included. Another >possibility is the quality of trials that got recruited were of low quality. Actually the systematic reviews had a lot of risk of bias, like no blinding, no proper detailing of randomization as well as whether concealed or not, early ending of the study after (usually unplanned) interim analysis as well as no prospective registration of trials. Further most of the trials used here had enrolled v few women for getting proper statistical power to find clinically important effect sizes, which is usually observed in our field [64]. Like in Endometrial Scratching, in two third of trials that reported LB had enrolled 200 women or<.Using 200 women in a trial would be the one that is powered to find a good and an improvement that is realistic via IVF add-ons of 20 %age points (like from 25-45%,at 80% power as well as 5% significant level.

Discussion

Thus here the usual IVF add-ons that have been suggested for making the Endometrial receptivity better and enhance the chances of implantation as well as pregnancy have been summarized, in view of weak proof to say that Vasodilators as well as G-CSF might lead to enhanced chances of pregnancy in certain women, heterogeneity, risk of bias as well as absence of data with regards to LBR prevents recommending these add-ons. Hence whatever proof is available points that whatever add-ons have been described do not have strong proof ,and need to be advised only in experimental setups like RCT's.

Problem lies in these add-ons being in routine use. The presence of this availability is not limited to just some clinics; but 74% of pts coming to fertility clinics in the UK got 1 or ≥1 add-ons in 2018 [2]. Thus clinicians tend to use these expensive add-ons for IVF without them having strong proof. ERA is utilized by IVF centres all over the world, though outcomes are not yet there from a single RCT that has been completed as yet. Reason seems to have multiple factors contributing. Probability is there that low quality of the initial primary work, most of which seems to show new add-ons to be of benefit, that can't be corroborated by new trials. Lot of add-ons therapies have been suggested to patients as probable therapies holding promise, and then there are suggestions to examine these by strong RCT's. Further no clear incentive is there for the companies to get better quality proof RCTs that might risk their products that they have already spread is of use. Researchers and academicians, not having experience enough can carry out small; biased RCT's and publish in peer reviewed journals, usually with no proper trial registration. The reason is most poor research comes as researchers are forced for their career prospective to conduct such research which is poorly equipped with them not getting stopped.

Little thought is given to the biological possibility in the development of new add-ons that usually seem to be on the basis of an misunderstanding of how implantation occurs. In the beginning intralipid was utilized as a placebo, in view of it having same looks, it was thought to be the control therapy for analyzing immunotherapy using syncytiotrophoblast membrane [22]. No clear reasonings are there for converting intralipid from placebo to a usual IVF adds ons. Getting newer IVF add-ons developed for enhancing endometrial receptivity need to be on the basis of a deep insight of the molecular as well as cellular processes taking place during implantation. Greater interaction among clinicians, reproductive biologist's immunologists might end in getting improved progress.

Further when clinicians are faced with the situation of RIF, they deeply want to increase pregnancy possibility and give something more. In case of poor prognosis or previous IVF failure, it might be thought by the clinicians that extra intervention might give probable advantage for conception. Further in a markedly commercial sector they are further stimulated by these people by the marketing as well as financial gains to give something that their competitors do not offer. Such interventions seem dangerous in the understanding that the vulnerable patients who might do including payment anything to get pregnancy.

Moreover clinicians who advocate add-ons need to also take into account the chances of harm. But one can't give an informed detailing of benefit versus harm if the proof of benefit is poor and that of harm even further bad. Maximum of the trials evaluating these interventions do not declare the side effects and rare but serious harms might not be easy to find. Like special fear is regarding congenital anomalies as well as prematurity from glucocorticoid exposure in pregnancy with any actual enhanced chances are checked only related to per implantation exposure via large cohort/ case controlled studies that have not been conducted. Other deleterious effects might be <serious but should not be ignored, including the side effects we know of, expenses to patients as well as probable psychological harms of giving wrong hope.

Limitations of this are only usually used add-ons considered. Other available immune therapies like tumor necrosisfactor alpha (TNF –α)-blockers tacrolimus as well as intrauterine injections of peripheral blood mononuclear cells are not taken into account. Most of cost factors come from specific countries like UK, US as well as Australia with prices conversion to US$ equivalent. Thus they may point cost information was not got systematically and might vary

in separate set ups.

Conclusion

Thus finally we have evaluated the present proof regarding usual IVF-add-ons that are pointed to enhance Endometrial receptivity like Immune therapies comprising of corticosteroids, Intravenous Immunoglobulin(IVIG) Granulocyte-Colony Stimulating Factor (G-CSF), as well as intralipid, Endometrial Scratching; Endometrial Receptivity Array (ERA); Uterine Artery Vasodilation including PRP as well as Intrauterine Human Chorionic Gonadotrophins (HCG). The results point that no strong proof is there that such add ones are efficacious or safe. A lot of them are very expensive, that may exhaust patients precious resources that might be utilized on better therapies or future more IVF's .Future large RCT's as well as proper safety exa mention needs to be a must before they get used during routine clinical practice.

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