Systematic Review

Evaluation Of Various Progesterone Therapy Routes For Luteal Phase Support In IVF: A Systematic Review And Meta-Analysis

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Abstract:

Background:

The progesterone secreted from the ovary until the seventh week of pregnancy is required to maintain pregnancy. In fertility-assisted cycles, administration of GnRH agonists can cause Corpus luteum failure, and progesterone secreted from the ovary will not be sufficient to protect pregnancy. The best way to prevent this situation is to support progesterone administration.

Objective: This study aimed to rank the best route of progesterone administration in luteal phase support.

Methods:

Randomized controlled trials (RCTs) of progesterone for the luteal phase support were identified from online databases of Scopus, Google Scholar, Pubmed. Treatment efficacy was defined as ongoing pregnancy. Data were extracted and analyzed using odds ratios (ORs). A Bayesian network meta-analysis was performed using the Markov chain Monte Carlo method in WinBUGS and NetMetaXL.

Results:

Total 1176 participants were studied in 16 trials of 6 separate progesterone routes including vaginal progesterone gel, progesterone sub q, Dydrogesterone, Cap 200 mg TID, Cap 200 mg BID, and progesterone IM. Comparison test shows better likelihood of SUCRA followed by vaginal progesterone gel (77.8%), progesterone sub q (55.49%), Dydrogesterone (53.97%), Cap 200 mg TID (50.67%), Cap 200 mg BID (48.99%) and finally progesterone IM (13.06%).

Conclusion:

This study ranked as the best route of progesterone therapy for luteal phase support, through the reviewed studies.

Keywords: Network meta-analysis, Progesterone, Luteal Phase Support, IVF.

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Introduction

In vitro fertilization (IVF) is a set of complex processes that comes with the help of fertility and help infertile people to perform the fertilization process properly (1–3). During IVF, the mature ovum is taken from the ovaries and fertilized by sperm in the laboratory. The fertilized ovum (embryo) or a set of ovum transferred to the uterus. A full cycle of IVF takes about three weeks. Sometimes these steps can be divided into several stages, and this process may take longer to complete(1,4,5). IVF is the most effective reproductive technology. The success of IVF treatment depends on many factors such as age and the causes of infertility. In addition, IVF can be time consuming, expensive and sometimes dangerous. If more than one embryo transfers into the uterus, IVF may lead to multiple pregnancies (2,4). The menstrual cycle is created to maintain fertility in women under the control of the endocrine system. This cycle is divided into three phases: Follicular phase, ovulation phase and luteal phase (6,7). The luteal phase in every woman's body begins at the end of ovulation time and ends the day before the next ovulation period. The luteal phase in the woman's body usually takes about 14 days. In this phase, the corpus luteum that is a structure grows on the surface of the ovaries, which release the mature ovum at the time of ovulation. The Corpus luteum, which produces the progesterone hormone in the woman's body(3,5,6). The progesterone hormone secreted from the corpus luteum makes the uterine wall suitable for the ovum Implantation process. This supportive effect of progesterone on the uterine wall is called luteal phase support. Luteal phase support is essential for IVF process success (1,3,6).

Table 1. Pregnancy rate in studies

	Vaginal gel	Cap 200 mg Tid	Pes 200 mg Bid	Dydrogesterone	IM	sub-Q
Geber (8)	44.26	36.07				
Simunic (9)	30.71	28.97				
Kleinstein (10)	22.17	25.23				
Tay (11)	36.11	34.55	34.29			
Ng (12)	34.29		30			
Ludwig (13)	28.77	18.87				
Tomic (14)	30.29			27.95		
Chi-hong ho (15)	56.72				33.77	
Lockwood (16)	29.07					27.43
Baker (17)	43.25					40.75
Zaman (18)	32.16				28.02	
Doblinger (19)	38.56					35.85
Yanushpolsky (20)	47.62				19.09	
Yanushpolsky (21)	45.15				42.29	
Chi (22)	40.19				34.13	
Berjis (23z)	15.58				18.82	

Sub-Q: Subcutaneous; IM: Intramuscular.

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Creating and strengthening luteal phase support is crucial to increase the success chance of the IVF process. Different forms of artificial progesterone types are used for this purpose. In this review and Network meta-analysis study, we aimed to compare the efficacy of different progesterone types used in luteal phase support in IVF.

Methods

Published randomized controlled trials (RCTs) are the eligible type of studies for inclusion. We do not include studies of inadequate randomization and studies with a lack of needed indexes. Studies with participation of infertile women trying to conceive by IVF method, and using any dose or route of progesterone administration as Intervention for Luteal phase support were included. Medication had to be administered after the day of ovulation.

Measured outcome

Ongoing pregnancy, as our main outcome, was defined as evidence of a 12-week fetal heart movement with gestational sac, confirmed by ultrasonography.

Search strategy

We searched for all published and RCTs evaluating luteal phase support in IVF/ICSI patients from 1990 to 2020. We developed the search strategy in consultation with the Cochrane Gynecology and Fertility (CGF) Group Information Specialists and then we searched in Google Scholar, PubMed, Science direct, etc. for eligible studies for analyses. In this study, IVF, luteal phase support progesterone and RCT were used as search keywords. We extracted data from included studies using a data extraction checklist designed and pilot-tested by our authors. We also extracted data on study characteristics as well as outcome data. When studies had multiple publications, we used the main trial report as the reference and then we derived additional details from secondary papers.

Statistical methods

WinBUGS program was used to perform a meta-analysis of the Bayesian network. Because the data sets given were dichotomous outcomes and included multi-arm trials, the study was focused on a binomial probability model which accounts for the use of multi-arm trials (7).

Table 2. Efficiency of various routs of progesterone therapy expressed by OR

Vaginal progesterone gel					
1.11 (0.77 – 1.59)	**subcutaneous progesterone**				
1.12 (0.57 – 2.16)	1.01 (0.47 – 2.13)	**Dydrogesterone**			
1.15 (0.78 – 1.63)	1.03 (0.62 – 1.71)	1.02 (0.49 – 2.26)	**Cap 200 mg TID**		
1.18 (0.50 – 2.59)	1.06 (0.42 – 2.61)	1.04 (0.37 – 3.03)	1.02 (0.44 – 2.36)	**Pes 200 mg BID**	
1.49 (1.12 – 2.08)	1.34 (0.84 – 2.25)	1.34 (0.66 – 2.86)	1.29 (0.83 – 2.17)	1.27 (0.56 – 3.30)	**progesterone IM**

Trials with zero cells in both arms and nodes with no occurrences have been excluded from the evidence networks as they do not convey information or need comprehensible details

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Meta-analyses were done for both fixed and random network effects, though the paradigm of fixed effects was used as the reference analysis Using the methodology of Markov Chain Monte Carlo, we predicted point figures and 95 percent reliable odds ratio (OR) intervals. In the consistency model, NetMetaXL often plots the posterior mean deviance of the single data points in the inconsistency model against their posterior mean deviance to find certain gaps in the interventions network where there is inconsistency.

Results

Finally, 1176 participants were studied in 16 trials of 6 separate progesterone routes including vaginal progesterone gel, subcutaneous progesterone, Dydrogesterone, Cap 200 mg TID, Pes 200 mg BID, and progesterone IM. The pregnancy rate in each study is shown for each arm in table 1 .

The efficiency of various routes of progesterone therapy expressed by OR is shown in table 2. The relative effectiveness is plotted as an OR with a credible interval of 95 percent. Based on these findings, we determined the surface under the cumulative ranking curve (SUCRA), which is the optimal transformed value according to the ranking of each therapy. Comparison test shows better likelihood of SUCRA followed by vaginal progesterone gel (77.8%), progesterone sub q (55.49%), Dydrogesterone (53.97%), Cap 200 mg TID (50.67%), Cap 200 mg BID (48.99%) and finally progesterone IM (13.06%). Table 3 displays every treatment scheme's SUCRA. A higher SUCRA score suggests better treatment outcomes based on the indirect form of contrast. Heterogeneity (OR: 21.8 percent, 95 percent CI: 2.3 – 56.9) was not significant and no inconsistency was seen as shown in figure 1.

Discussion

Progesterone is available in many different forms, including vaginal micronized gel, vaginal suppository, oral tablets and injectable progesterone are widely used in the world. Intra-muscular progesterone is an oily compound that needs daily injections, whereas progesterone suppositories can be used in the rectum or vaginal direction to support the luteal phase. Muscle administration increases the serum progesterone level, but vaginal administration of the progesterone causes up to a 3-fold greater level of the drug than that obtained with intramuscular administration in the endometrial tissue. Dihydrogestron (Dofastone) is used in people with luteal phase deficiency and treatment for recurrent miscarriages. Its molecular structure and pharmacology resemble endogenous progesterone, although its oral dosage forms the same activity as endogenous progesterone. Many clinical trials have been published on the comparison of different routes of progesterone therapy in luteal phase support and subsequently, many meta-analysis studies have investigated these massive data. Part of the studies has focused on progesterone therapy along with human chorionic gonadotropin (hCG) or each of those alone (24).

Table 3. SUCRA score of

Treatment	SUCRA
Vaginal progesterone gel	0.7782
Subcutaneous progesterone	0.5549
Dydrogesterone	0.5397
Cap 200 mg TID	0.5067
Cap 200 mg BID	0.4899
IM progesterone	0.1306

Our study with a network meta-analysis methodology revealed that Vaginal progesterone gel had the best ranked between

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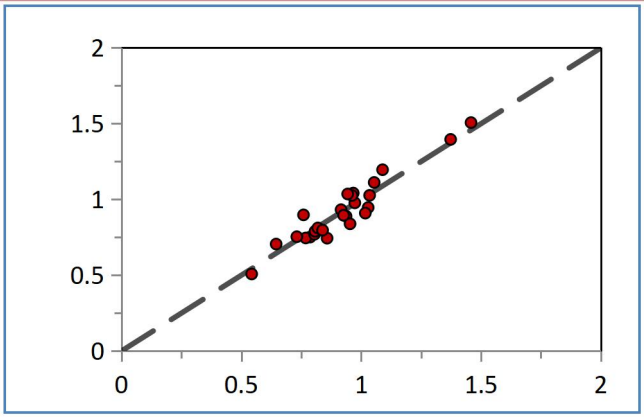

Figure 1. Consistency model of study

other routes in evaluated studies while IM form had the least response to treatment; While a meta-analysis study by Pritts et al. revealed that IM progesterone is preferred to oral or vaginal route (25).

Injection form requires daily injections and may cause inflammatory reactions and rarely sterile abscesses, but its price is much cheaper than vaginal capsule formulation. In the vaginal method, it is easy to use and allergic reactions are rare but unfortunately, the cost is high (26).

In another meta-analysis conducted by Watters et al., short versus extended progesterones were compared and prologued progesterone therapy was not considered to be necessary; while we did not assess progesterone cessation time in our study, which might be a confounding factor (27).

Another study, reviewing two studies, reported better efficiency of IVF outcomes in patients receiving oral dydrogesterone versus patients micronized vaginal progesterone (28); while in our study, better efficiency of vaginal progesterone was seen. our study revealed vaginal progesterone is superior to other routes; while Salehpour et al. (29) found no differences.

Conclusion

This study ranked as the best route of progesterone therapy for luteal phase support, through the reviewed studies; while there were lots of confounding factors and limitations due to the various dosing used in different studies.

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