Subcutaneous progesterone is effective and safe for luteal phase support in IVF: An individual patient data meta-analysis of the phase III trials.

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Study Question

To summarize efficacy and safety of subcutaneous (s.c.) progesterone as compared to vaginally administered progesterone for luteal phase support in patients undergoing IVF.

Summary Answer

No statistical significant or clinical significant differences exist between subcutaneous and vaginal progesterone for luteal phase support.

What is known already

A recent Cochrane review reported that luteal phase support with progesterone is associated with higher rates of live birth or ongoing pregnancy as compared to placebo. Two large phase III studies (07EU/Prg06 and 07USA/Prg05) on s.c. progesterone were finalized in 2013. Both studies were designed and conducted to establish non-inferiority of ongoing pregnancy likelihood in patients undergoing IVF or ICSI and receiving luteal phase support with daily s.c. injections of 25 mg progesterone as compared to vaginally administered progesterone gel or progesterone tablets. Each study showed non-inferiority of s.c. progesterone in relation to vaginal progesterone.

Study design, size, duration

This meta-analysis collates data from two phase III trials (07EU/Prg06, NCT00827983; 07USA/Prg05, NCT00828191) performed according to GCP standards, resulting in a total sample size of 1483 randomized patients, 1435 of whom underwent embryo transfer. Outcomes of interest were ongoing pregnancy rate, live birth rate and OHSS risk. Analysis was performed on the level of individual patient data. A comprehensive literature search revealed no further randomized studies on s.c. progesterone usage in IVF.

Participants/materials, setting, methods

A sample size of 1,483 women between 18 and 42 were included in the study. In both studies inclusion criteria were similar, e.g. BMI <30kg/m^2, <3 prior ART cycles (IVF, ICSI and related procedures), baseline (cycle day 2 or 3) FSH <15 IU/L and E_2 <80 pg/mL, normal uterine cavity as per recent hysterosalpingogram, sonohysterogram or hysteroscopic exam (i.e. no polyp or protruding sub-mucosal fibroid), at least 3 retrieved oocytes and written informed consent.

Main results and the role of chance

The administration of subcutaneous progesterone versus intra-vaginal progesterone had no impact on ongoing pregnancy likelihood (OR=0.865, 95% CI 0.694 to 1.077; P=n.s.), live birth likelihood (OR=0.889, 95% CI 0.714 to 1.106; P=n.s.) (Table 1) or OHSS risk (OR=0.995, 95% CI 0.565 to 1.754; P=n.s.) in regression analyses accounting for clustering of patients within trials, while adjusting for important confounders. Only female age and number of oocytes retrieved were significant predictors of live birth likelihood and OHSS risk.

Limitations, reasons for caution

Licensing studies are conducted in a selected patient population and the external validity of the findings is limited to similar cohorts in daily practice. Furthermore, only IVF cycles with fresh ET were included in the two phase III studies.

Wider implications of these findings

Subcutaneous progesterone 25 mg/day for luteal phase support is as efficacious and safe as vaginal progesterone gel or tablets. Accordingly, s.c. progesterone represents a valid alternative to vaginally applied progesterone.

Table 1: Predictors of live birth after progesterone treatment. Figures are numbers (percentages) unless stated otherwise.

	Live birth		Odds ratio (95% CI)	
Parameters	Yes	No	Crude	Adjusted
Randomised treatment:				
Progesterone s.c. vs Progesterone vaginal	252/523 (48.18)	462/912 (50.66)	0.900 (0.725 to 1.118)	0.889 (0.714 to 1.106)
Progesterone vaginal	271/523 (51.82)	450/912 (49.34)	1	1
Median (IQR) age of woman (yrs)	33.00 (30.00-36.00)	34.00 (31.00-38.00)	0.940 (0.917 to 0.964)[a]	0.945 (0.920 to 0.970)
Median (IQR) BMI of woman	22.85 (21.00 to 25.25)	22.79 (20.66 to 25.52)	0.996 (0.962 to 1.032)	-
Median (IQR) duration of infertility (months)	34.00 (20.00 to 48.00)	36.00 (22.00 to 51.00)	1.000 (0.997 to 1.004)	-
Type of treatment				-
IVF vs Both	130/523 (24.86)	261/912 (28.62)	0.851 (0.584 to 1.240)	
ICSI vs Both	322/523 (61.57)	548/912 (60.09)	1.040 (0.737 to 1.467)	
Both	71/523 (13.58)	103/912 (11.29)	1	
Primary cause of infertility				-
Female vs Unexplained	155/523 (29.64)	250/912 (27.41)	1.225 (0.858 to 1.748)	
Male vs Unexplained	198/523 (37.86)	363/912 (39.80)	1.199 (0.852 to 1.687)	
Combined vs Unexplained	102/523 (19.50)	159/912 (17.43)	1.407 (0.956 to 2.070)	
Unexplained	68/523 (13.00)	140/912 (15.35)	1	
Median (IQR) endometrial thickness (mm)	11.00 (9.80 to 12.30)	10.80 (9.30 to 12.00)	1.054 (1.007 to 1.103) [9b]	-
Previous children				-
Yes	159/523 (30.40)	281/912 (30.81)	1	
No vs Yes	364/523 (69.60)	631/912 (69.19)	0.983 (0.776 to 1.244)	
Median (IQR) baseline FSH level (IU/l)	6.70 (5.60 to 8.08)	6.81 (5.60 to 8.10)	0.970 (0.922 to 1.021)	-
Median (IQR) No. of oocytes retrieved	13.00 (9.00 to18.00)	11.00 (7.00-16.00)	1.021 (1.006 to 1.037)[9c]	1.012 (0.996 to 1.028)
Median (IQR) No. of embryos transferred	2.00	2.00 (2.00 to 3.00)	0.888 (0.762 to 1.034)	-
Transfer difficulty				-
Easy vs Moderately difficult	498/522 (95.40)	835/909 (91.86)	1.645 (1.008 to 2.684)	
Moderately difficult	23/522 (4.41)	69/909 (7.59)	1	
Extremely difficult vs Moderately difficult	1/522 (0.19)	5/909 (0.55)	0.570 (0.063 to 5.199)	

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