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ORIGINAL ARTICLE

Prospective, randomized study to evaluate the success rates using hCG, vaginal progesterone or a combination of both for luteal phase support

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Background. A prospective study was done to compare the efficacy of luteal phase support (LPS) using either three times hCG (group I, $n=77$), hCG on the day of embryo transfer (ET) in combination with daily vaginal progesterone (group II, $n=62$) or vaginal progesterone only (group III, $n=70$).
Method. All patients were treated using the long luteal protocol for controlled ovarian stimulation in an IVF (*in vitro* fertilization) cycle. Patients were randomized to one of these groups when estradiol was <2500 pg/ml and less than 12 oocytes were retrieved (low risk groups). If estradiol was ≥ 2500 pg/ml and/or at least 12 oocytes were retrieved (high risk groups), patients were randomized to receive either hCG in combination with daily vaginal progesterone (group IV, $n=83$) or progesterone only (group V, $n=121$). For vaginal progesterone Utrogest® was used (three times daily two capsules containing 100 mg progesterone, 600 mg/d).
Results. Demographic data were comparable within the high risk and low risk groups. However, for unknown reasons the fertilization rate was significantly higher in group V (48%) compared to group IV (40%) ($p<0.05$), leading to a significantly higher cumulative embryo score. There were no statistically significant differences with regard to the main outcome parameter, the clinical ongoing pregnancy rate in the low risk groups (14.3%, 14.5%, 11.4%) and the high risk groups (21.0%, 21.5%), respectively. Using a standardized discomfort scale, there were more complaints towards the end of the luteal phase in the groups receiving hCG only or an additional injection of hCG, when compared to the progesterone only groups.
Conclusion. Progesterone only for luteal phase support leads to the same clinical ongoing pregnancy rate as hCG, but has no impact on the comfort of the patient.

Key words: hCG; luteal phase support; progesterone

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Luteal phase support (LPS) is proposed to be a necessary tool in controlled ovarian stimulation (COS) especially in IVF (*in vitro* fertilization) cycles which are stimulated according to the long protocol (26). Several protocols are used for LPS, which vary from center to center according to the substances used or the way of administration.

Currently LPS is used three ways, either progesterone alone, hCG, or a combination of both. Progesterone has been administered orally (14, 15), intramuscularly (3, 10) or vaginally (15, 24, 25).

Abbreviations:
IVF: *in vitro* fertilization; LPS: luteal phase support; ET: embryo transfer; COS: controlled ovarian stimulation; ICSI: intracytoplasmic sperm injection; OHSS: ovarian hyperstimulation syndrome.

Until now, no prospective randomized study has been published, which compared either vaginal progesterone and hCG directly, or the combination of hCG and progesterone with one of the two other protocols.

In two previous studies the outcome of progesterone in one group and hCG in the other group was compared (7, 14). In these studies, however, progesterone was given as an oral medication, which has been shown to be much less effective compared to a vaginal or intramuscular administration (9, 15).

Since it is a well known fact that hCG increases the risk of ovarian hyperstimulation syndrome (OHSS) (3, 6, 19, 22) and has some discomfort for the patients, we designed this trial to compare the success rates of all three protcols.

Material and methods

Inclusion, exclusion criteria and ethical considerations

Four hundred and thirteen patients were randomized prospectively to one of the three protocols as described below. Only patients up to 40 years of age who underwent COS for IVF or IVF/ICSI were included (*in vitro* fertilization/intracytoplasmic sperm injection). All these patients, if they had a successful oocyte pick up, were asked for written informed consent and were subsequently randomized according to a randomization list. Abdominal discomfort on the day of ET as a sign of a beginning OHSS and estradiol levels above 5.000 pg/ml were exclusion criteria. The protocol was approved by the Ethics Board of the Medical University of Lübeck.

Controlled ovarian stimulation

COS was done according to the long luteal protocol in all cases, using a GnRH agonist depot formulation and either recFSH (Gonal F 75, Serono Pharma GmbH, Munich, Germany), or hMG (Menogon, Ferring Arzneimittel GmbH, Kiel, Germany). IVF and/or ICSI was done according to the center's rule and as described previously (2). Ovulation induction was done with 10.000 IU hCG i.m. when the leading follicle had a size of 18 to 22 mm. Cryopreservation was done always at the 2 pronuclear (2 PN) stage, according to the German Embryo Protection Law (16), as previously described (1).

Cumulative embryo score

The cumulative embryo score, as published by Steer et al. (27), was slightly modified, since we do not use four but three different degrees of embryo quality. The quality score of a single embryo was calculated as the product of the number of its blastomeres and the degree of its quality (1: fair, 2: moderate, 3: ideal). The cumulative embryo score is calculated as the sum of all single embryo scores.

Luteal phase support protocols

There were two risk categories – low risk and high risk –to which the patients were stratified. In the low risk category (groups I, II, III) only those patients were randomized who had <12 oocytes retrieved and <2.500 pg/ml estradiol on the day of ovulation induction. In the high risk category (groups IV and V) those patients were randomized who had ≥12 oocytes and/or ≥2.500 pg/ml estradiol on the day of ovulation induction.

Patients in group I received 5.000 IU hCG on the day of ET, and 5.000 IU and 2.500 IU three and six days later. Patients in group II received 5.000 IU hCG on the day of ET and started with the vaginal administration of progesterone on the evening before ET (200 mg three times a day, Utrogest®, Dr. Kade, Berlin, Germany) until either menstrual bleeding occurred or the pregnancy test showed a positive result. Patients in group III received only vaginal progesterone according to protocol of group II. Patients in group IV received 5.000 IU hCG on the day of ET and started with the vaginal administration of progesterone on the evening before ET. The protocol in group IV was therefore the same as in group II. Patients in group V received only progesterone, starting on the evening before ET, i.e. the same protocol as the patients in group III. The randomization is also shown in Fig. 1.

Since patients at high risk for the development of a severe OHSS (estradiol >5.000 pg/ml and/or complaints of an OHSS as early as on the day of ET) were excluded from this study, it seems ethically permissible for us to inject hCG also once in the high risk group. This was, furthermore, general practice in our department for years and is prac-

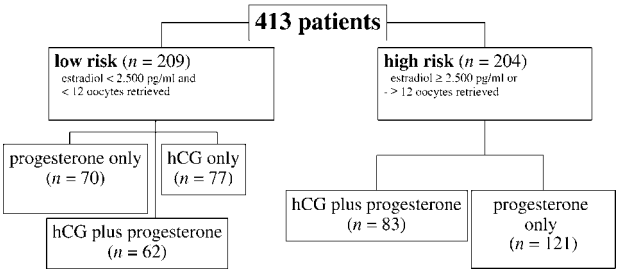

Fig. 1. Randomization scheme of the study

ticed worldwide in several centers. Also this approach was approved by the Ethics Board of the University of Lübeck.

Pregnancies

Only pregnancies with positive fetal heartbeats were included as clinical pregnancies. Those pregnancies which resulted in a delivery of a liveborn or stillborn child above 500 g body weight or of a liveborn child below 500 g body weight, were counted as ongoing pregnancies. All other pregnancies were counted as abortions.

Psychosomatic profile of the patients

Seventy-nine subsequent patients filled out a questionnaire on each day according to the Befindlichkeits-Skala (28). The data of 71 of the questionnaires could be included in this study. On each day of the luteal phase one questionnaire was filled out, each daily questionnaire consisted of 24 items, two different questionnaires were used, which changed every other day. The test has proved itself to be useful for determination of psychosomatic complaints during a pharmacological treatment and is described elsewhere in detail (28).

Statistical analysis

Statistics were done using Chi-square test, Mann-Whitney-test, and Kruskal Wallis test. Correlation coefficients were calculated according to Pearson. Data were analyzed using SPSS 9.0 (SPSS, Chicago, Ill.).

Results

Four hundred and thirteen patients were randomized in this study. The demographic data of these patients are shown in Table I. Within each risk category there were no statistically significant differences between the three and two arms, respectively. However, the patients in the high risk group had a significantly lower age, a significantly longer menstrual cycle, and were more likely to have a primary infertility when compared to the low risk group ($p<0.01$). The rate of oligomenorrhea was higher in the group of patients with a high risk ($p<0.05$).

In Table II the data regarding the stimulation cycles are shown. Within the low risk group the number of oocytes retrieved was significantly lower (6.16±3.41) in group II (hCG+P) when compared to group I (hCG) (7.19±2.58) and group III (P) (7.44±3.00) ($p<0.05$). The number of previous IVF cycles and the cumulative dose of gonadotrophins used was significantly lower in groups IV (hCG+P) and V (P) compared to groups I (hCG), II (hCG+P), and III (P) ($p<0.05$). More cases of OHSS °III were described in the high risk group compared to the low risk group. This difference was not statistically significant. Whenever hCG was applied in the low risk group (group I) or the high risk group (group IV), the risk of OHSS °III was slightly higher compared to the other groups (not statistically significant). The overall number of oocytes retrieved and the number injected or inseminated was significantly higher in the high risk groups compared to the low risk group ($p<0.05$), but the fertilization rate was significantly higher in the low risk group ($p<0.01$). As a consequence of the higher number of oocytes, there were more cryopreserved oocytes at the 2 pronuclear stage ($p<0.01$) and more embryos transferred ($p<0.05$) with a higher cumulative embryo score ($p<0.01$) in the high risk group compared to the low risk group. Interestingly, there was a significantly higher fertilization rate in group V (P) compared to group IV (hCG+P) (48% *vs.* 40%, $p<0.01$), re-

Table I. Demographic data of all patients, included in the study

	Low risk			High risk		
Group	Group I (hCG)	Group II (hCG+P$^+$)	Group III (P only)	Group IV (hCG+P)	Group V (P only)	Total
n	77	62	70	83	121	413
Age [years] [1]	33.17±3.58	33.82±4.09	32.86±4.43	31.13±3.91	30.97±3.70	32.16±4.06
Body mass index [kg/m^2]	23.70±0.04	24.14±0.04	24.92±0.05	24.58±0.05	24.02±0.04	24.24±0.04
Length of natural cycle [d][1]	29.32±7.99	28.40±2.51	31.15±19.16	32.34±17.64	31.84±13.30	30.85±13.80
Presence of amenorrhea [%]	–	1.7	–	–	0.8	0.5
Presence of oligomenorrhea [%][2]	3.9	–	4.3	9.6	6.7	5.4
Primary infertility [%][1]	45.5	62.9	54.3	69.9	66.9	60.8
ICSI cycles [%]	98.7	98.4	100	97.6	98.3	98.5

[1] $p<0.01$ for high risk *vs.* low risk group.
[2] $p<0.05$ for high risk *vs.* low risk group.
$^+$ progesterone.

Table II. Stimulation cycles and embryo transfers

Group	Low risk			High risk		Total
	Group I (hCG)	Group II (hCG+P$^+$)	Group III (P only)	Group IV (hCG+P)	Group V (P only)	
n	77	62	70	83	121	413
No. of previous cycles[2]	2.66±1.39	2.68±1.99	2.34±1.55	2.31±1.35	2.16±1.36	2.39±1.15
Days of gonadotrophins	14.65±2.15	14.91±3.11	15.37±2.58	14.79±3.18	14.22±2.67	14.72±2.77
Cumulative dose of gonadotrophins [IU][2]	4266±1610	4247±2024	4263±1513	3286±1029	3106±1316	3731±1574
Estradiol on hCG day [pg/ml][3]	1305±533	1202±576	1408±590	2534±896[4]	2677±984	1953±1018
OHSS °I	11.7	6.5	8.6	12.0	14.9	11.4
OHSS °II	5.2	3.2	5.7	2.4	1.7	3.4
OHSS °III	2.6	1.6	1.4	4.8	2.5	2.7
Oocytes retrieved[2]	7.19±2.58	6.16±3.41$^+$	7.44±3.00	14.39±4.31	14.69±4.80	10.72±5.42
Oocytes inseminated/injected[2]	6.65±2.68	5.82±3.38	6.77±3.06	13.28±4.26	13.53±4.63	9.89±5.17
Fertilization rate [%][3]	51.85	56.25	47.75	40.22[1]	48.42[1]	48.47
No. cryopreserved*[3]	0.55±1.29	0.34±1.12	0.26±0.86	2.60±3.63[1]	3.32±3.24[1]	1.69±2.85
Cumulative embryo score[3]	23.01±9.98	21.02±11.75	24.01±11.07	25.39±12.56[1]	29.03±10.07[1]	25.11±11.33
No. of embryos/transfer[2]	2.61±0.67	2.39±0.82	2.57±0.73	2.77±0.55	2.88±0.37	2.68±0.63

* according to the German Embryo Protection Law only oocytes at the pronuclear stage were cryopreserved.
$^+p<0.05$ for number of oocytes retrieved (group II *vs.* group I and group III).
[1] $p<0.01$ (fertilization rate) and $p<0.05$ (number cryopreserved and cumulative embryo score).
[2] $p<0.05$ for low risk *vs.* high risk group.
[3] $p<0.01$ for low risk *vs.* high risk group.
[4] from two patients in this group (IV) there were no estradiol levels available on the day of hCG administration.

Table III. Outcome of transfer cycles

Group	Low risk			High risk		Total
	Group I (hCG)	Group II (hCG+P)	Group III (P only)	Group IV (hCG+P)	Group V (P only)	
n	77	62	70	83	121	413
Implantation rate per transferred embryo [%]	9.95	11.82	8.57	13.45	14.04	11.90
Child delivered per transferred embryo [%]	6.47	7.43	5.00	6.96	9.46	7.40
Total clinical pregnancy rate per transfer [%]*	19.5	21.0	18.6	27.7	28.1	23.7
Extrauterine pregnancy rate per transfer [%]	2.6	–	2.9	2.4	–	1.5
Heterotopic pregnancy rate per transfer [%]	–	–	–	1.2	1.7	0.7
Multiple pregnancy rate per total no. of pregnancies [%][1]	20.0	23.0	7.7	4.4	17.7	14.3
Abortion rate per clinical pregnancies [%]	15.4	30.8	27.3	10.0	18.8	19.1
Ongoing clinical pregnancy rate per embryo transfer [%]	14.3	14.5	11.4	21.0	21.5	17.4

*total number of clinical pregnancies without heterotopic and ectopic pregnancies.
[1] $p<0.01$ for low risk *vs.* high risk group.

sulting also in a significantly higher number of cryopreserved oocytes at the 2 PN stage ($p<0.05$) and a significantly higher cumulative embryo score ($p<0.05$).

Table III summarizes the outcome parameters of the transfer cycles. The implantation rates and clinical ongoing pregnancy rates were not significantly different between the different groups. The pregnancy rates were higher in the high risk compared to the low risk group, but this difference was not statistically significant. However, there was a significantly higher multiple pregnancy rate per total number of pregnancies in the low risk compared to the high risk group ($p<0.01$).

The numbers regarding the pregnancy complications and delivery data in the different groups were too small to be a subject to statistical analyses (Table IVa). The data of delivered singletons and twins are shown in Table IVb. Statistically significant differences could be described for body weight, body length, and gestational age ($p<0.01$), as well as for the mode of delivery ($p<0.05$). No stillborn infants were noted.

To test if the pregnancy rates in the different groups were correlated to the estradiol levels on the day of hCG, we calculated the different pregnancy rates regarding several cut off levels (1000 pg/ml, 1500 pg/ml, 2000 pg/ml). These values were shown in Table V. No statistically significant differences were seen.

The pregnancy rates depending on the estradiol levels per retrieved oocytes were also calculated (Table VI). With no cut off values a significant difference between the clinical ongoing pregnancy rate was seen.

By chance, only four patients in group II received a questionnaire, since consequently over the period of two months 79 questionnaires were distributed to the patients. Therefore, only groups I (n=21), III (n=15), IV (n=13), and V (n=22)

Table IV. Pregnancy course (a) and pregnancy outcome parameters differentiated with respect to singleton and twin pregnancies (b). No higher order pregnancy rates were recorded

(a)

	Low risk			High risk		
Group	Group I (hCG)	Group II (hCG+P$^+$)	Group III (P only)	Group IV (hCG+P)	Group V (P only)	Total
n	77	62	70	83	121	413
Male/female	0.56	0.43	0.33	0.73	0.57	0.53
Pregnancy induced hypertension # [%]	20.0	20.0	–	5.9	8.3	10.3
Preeclampsia # [%]	–	11.1	–	–	–	1.5
HELLP syndrome # [%]	–	–	–	–	4.2	1.5
Gestational diabetes # [%]	–	11.1	–	23.5	4.2	8.8
Bleeding in pregnancy <28. weeks of gestation # [%]	30.0	11.1	–	12.5	20.8	14.7
Gestational age at delivery [weeks]	36.57±3.72	38.46±1.63	36.77±5.46	38.95±2.95	38.49±2.34	38.11±3.16

#per ongoing pregnancy.

(b)

Parameter	Singletons	Twins
n	53	15
Body weight [g] [1]	3205±598	2300±455
Body length [cm] [1]	51.0±3.2	47.7±3.4
Gestational age[1]	38.7±3.1	36.1±2.7
Mode of delivery		
Spontaneous [%][2]	65.4 (34)	28.6 (4)*
Cesarean section [%][2]	34.6 (18)	71.4 (10)

*one second born twin was delivered by forceps. [1]p<0.01 and [2]p<0.05 for singletons *vs.* twins.

Table V. Pregnancy rate depending on the kind of luteal phase support and the estradiol level on the day of hCG administration. From two patients of group IV, estradiol levels were not available for this analysis

		Clinical ongoing pregnancy rate (COPR) [%] (*n*)					
		Low risk			High risk		
Parameter		1	2	3	4	5	Total
Estradiol < 1000 pg/ml	*n*	23	23	18	1	4	69
	COPR % (n)	4.3 (1)	17.4 (4)	16.7 (3)	0 (0)	0 (0)	11.6 (8)
Estradiol ≥ 1000 pg/ml	*n*	54	39	52	80	117	344
	COPR % (n)	18.5 (10)	12.8 (5)	9.6 (5)	21.3 (17)	22.2 (26)	18.3 (63)
Estradiol <1500 pg/ml	*n*	47	45	40	8	14	154
	COPR % (n)	8.5 (4)	15.6 (7)	12.5 (5)	25 (2)	21.4 (3)	13.6 (21)
Estradiol ≥ 1500 pg/ml	*n*	30	17	30	73	107	257
	COPR % (n)	23.3 (7)	11.8 (2)	10.0 (3)	20.5 (15)	21.5 (23)	19.5 (50)
Estradiol < 2000 pg/ml	*n*	68	54	57	24	31	234
	COPR % (n)	11.7 (8)	14.8 (8)	12.3 (7)	25 (6)	22.3 (7)	15.4 (36)
Estradiol ≥ 2000 pg/ml	*n*	9	8	13	57	90	177
	COPR % (n)	33.3 (3)	12.5 (1)	7.7 (1)	19.3 (11)	21.1 (19)	19.8 (35)
Total	*n*	77	62	70	81	121	411
	COPR % (n)	14.3 (11)	14.5 (9)	11.4 (8)	21.0 (17)	21.5 (26)	17.2 (71)

Table VI. Pregnancy rate depending on the kind of luteal phase support and the concentration of estradiol per retrieved oocyte. From two patients of group IV, estradiol levels were not available for this analysis

		Clinical ongoing pregnancy rate [%] (n)					
		Low risk			High risk		
Parameter		1	2	3	4	5	Total
Estradiol/oocyte <100 pg/ml	*n*	5	5	2	7	12	31
	COPR % (n)	0 (0)	40 (2)	50 (1)	29 (2)	17 (2)	23 (7)
Estradiol/oocyte 100–149 pg/ml	*n*	14	15	17	18	24	88
	COPR % (n)	7 (1)	20 (3)	18 (3)	33 (6)	21 (5)	20 (18)
Estradiol/oocyte 150–199 pg/ml	*n*	25	6	13	18	31	93
	COPR % (n)	12 (3)	17 (1)	0 (0)	11 (2)	26 (8)	15 (14)
Estradiol/oocyte 200–249 pg/ml	*n*	13	16	18	17	13	77
	COPR % (n)	23 (3)	0 (0)	11 (2)	29 (5)	8 (1)	14 (11)
Estradiol/oocyte 250–299 pg/ml	*n*	5	4	6	7	17	39
	COPR % (n)	0 (0)	25 (1)	17 (1)	0 (0)	18 (3)	13 (5)
Estradiol/oocyte ≥300 pg/ml	*n*	15	16	14	14	24	83
	COPR % (n)	27 (4)	13 (2)	7 (1)	14 (2)	29 (7)	19 (16)
Estradiol/oocyte <150 pg/ml	*n*	19	20	19	25	36	119
	COPR % (n)	5 (1)	25 (5)	21 (4)	32 (8)	19 (7)	21 (25)
Estradiol/oocyte 150–249 pg/ml	*n*	38	22	31	35	44	170
	COPR % (n)	16 (6)	5 (1)	6 (2)	20 (7)	20 (9)	15 (25)
Estradiol/oocyte ≥250 pg/ml	*n*	20	20	20	21	41	122
	COPR % (n)	20 (4)	15 (3)	10 (2)	10 (2)	24 (10)	17 (21)
Total	*n*	77	62	70	81	121	411
	COPR % (n)	11	9	8	17	26	17 (71)

could be analyzed for the psychological profiles. Four questionnaires were not sent back by the patients. In group III (P) there was no change of subjective estimation of discomfort over the whole luteal phase (Fig. 2). There was also no difference between pregnant and non pregnant patients from all groups (data not shown). In group V (P), a significant correlation towards less complaints to the end of the luteal phase could be described ($r = -0.66$, $p < 0.01$). The most frequent complaints were very similiar in all four groups, and included tiredness, abdominal pain and breast tenderness.

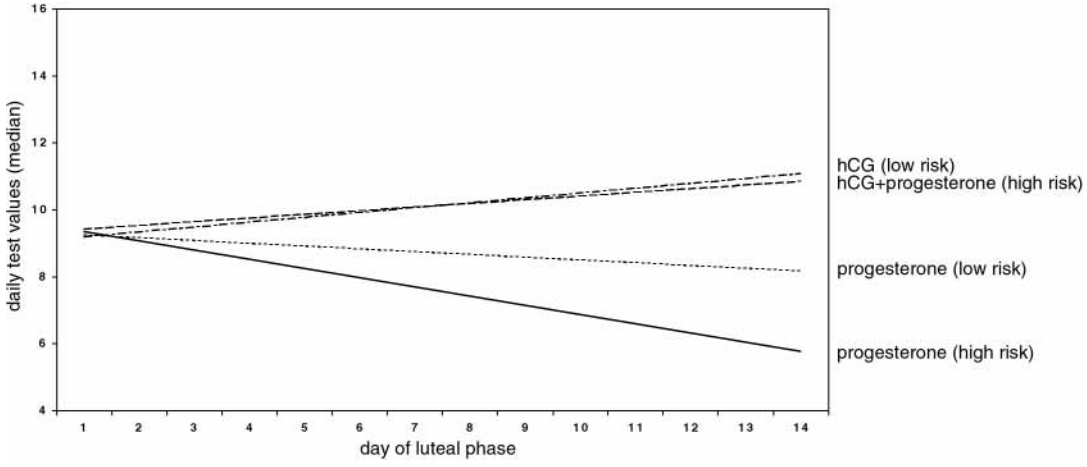

Fig. 2. Median values in dependence of the luteal phase protocol. The only trend towards more complaints during the luteal phase was observed in those patients, who received three times hCG injections (- – – -) or a single hCG injection additionally to progesterone in the high risk group (– – –). Patients in the high risk progesterone group showed a significantly reduced discomfort score throughout the luteal phase (——) (r=-0.66, $p<0.01$), patients in the low risk progesterone group (- – - – -) showed no trend towards more or less complaints.

Discussion

Since the introduction of the long protocols in COS the necessity of LPS has been shown several times (26). It was proved, that in fact endometrial transformation is better after sufficient luteal phase support (5). In this study we have shown that there is no statistical significant difference either in pregnancy rates or in implantation rates, when either multiple doses of hCG, a single hCG dose in combination with vaginal progesterone or vaginal progesterone alone were used for LPS. This study, for the first time, directly compared a protocol including hCG administration with the vaginal administration of progesterone and a combination of both regimens.

Cycle length, the presence of oligomenorrhea and the percentage of primary infertility were significantly higher in the high risk group. These are well known risk factors for a good response in controlled ovarian stimulation procedures. A longer cycle length and oligomenorrhea especially may identify the subset of patients who suffer from polycystic ovarian syndrome (PCOS) (11, 17). A younger age is also a known risk factor for a high response (20, 21). A lower number of previous IVF cycles in the high risk group correlates well with the presence of a good response to the stimulation procedure. Therefore all these differences could be expected.

The data regarding the stimulation cycles themselves show a lower cumulative dose of gonadotrophins in the high risk group – which correlates well with the good response in this group. It could be expected that estradiol levels and the number of oocytes retrieved were significantly higher in the high risk group, since these were the parameters for the initial stratification. As a consequence of the higher number of oocytes retrieved there were significantly more inseminated or injected oocytes and oocytes, which were cryopreserved at the 2 PN stage, more embryos per transfer and a significantly higher cumulative embryo score in the high risk group. The course of pregnancy and pregnancy complications were not influenced by the way of luteal phase support. The data, especially of pregnancy complications, however, are too small to be analyzed statistically.

Interestingly, in group IV (hCG+P) there was a significantly lower fertilization rate (40% *vs.* 48%, $p<0.05$), resulting in a significantly lower number of 2 PN oocytes, which were cryopreserved and a significantly lower mean cumulative embryo score ($p<0.01$), because this directly depends on the number of embryos available for transfer. There is no explanation for this phenomenon, especially because the randomization procedure has shown comparable groups of patients in the high risk group (Table I). However, it is important to remark that maybe this might have influenced the outcome parameters. The implantation rate per transferred embryo, the percentage of children delivered per transferred embryo, as well as the ongoing clinical pregnancy rate, were always somewhat higher in the progesterone-only group (group V), when compared to group IV (hCG+P). It is possible that these differences would not have appeared when the differences in the fertilization rate, and especially the cumulative embryo scores, would not have been present. Even if this is a prospective, randomized study, this difference in the outcome parameters should be kept in mind. Finally, however, it can be expected that even with similar fertilization rates the clinical ongoing pregnancy rates would have been comparably high.

The vaginal route of progesterone administration has the great advantage that this physiological substance is transported directly to the endometrium (9) and no metabolic changes are done to this steroid (first uterine pass effect) (12). It has been shown recently that in fact similar progesterone serum levels are achieved using either orally administered progesterone (600 mg/day), or intramuscularly administered progesterone (50 mg), but that endometrial changes were observed more appropriately with intramuscularly administered progesterone (15). Similiar observations could be done with nasal administered progesterone (8). Furthermore, with vaginal progesterone the histologic endometrial changes are more in phase compared to orally administered or intramuscularly administered progesterone (4).

The problem of hCG administration for luteal phase support is the higher risk of OHSS with the subsequent development of ascites, pleural effusions, thrombo-embolic complications (13, 23) or even myocardial infarction (18). Even if these complications are rare, they are possibly life-threatening and should be avoided as far as possible. Since hCG is a well known risk factor for the development of OHSS it should be withheld whenever possible.

In the present study there was no statistically significant difference in pregnancy rates depending on the estradiol level on the day of hCG administration, when different cut off values were used (Table IV). The numbers per group, however, were quite small. Most important, however, was the finding that with higher estradiol levels – independent from the chosen cut off value – there was a higher clinical ongoing pregnancy rate. This must be interpreted in this way, so that even in cases of low estradiol levels there is no argument in favor of hCG administration for luteal phase support.

This is reassured by the data from Table VI. None of the pregnancy rates in the different subgroups were statistically significantly different. However, only in group I, when patients only received hCG, was there a trend towards lower pregnancy rates in those patients, who had a lower estradiol per oocyte ratio. This finding was in contrast to the other two groups in the low risk category: here the pregnancy rates were highest in the low estradiol per oocyte ratio group. It can be speculated that in this low estradiol group the lower estradiol levels are caused by a disturbed follicular maturation. This results in a granulosa cell defect with low estradiol levels. The developing corpus luteum, which consists of large luteal cells – developing from the granulosa cells – and small luteal cells – developing from the theca cells, may have the same steroid synthesis defect. Therefore, the administration of hCG for luteal phase support in these patients might be ineffective: the disturbed corpus luteum function cannot be rescued, since it is not able to produce enough progesterone even when stimulated by exogenous gonadotropins. The only way to achieve a sufficiently high progesterone level is by the administration of natural progesterone. This hypothesis, however, must be investigated by further studies with a larger number of patients. It should be kept in mind that the observed differences in pregnancy rates just exist by chance and are the result of the small number of pregnancies per group.

The single dose administration of hCG had no advantage for the subsequent pregnancy rate in this study, when compared with a luteal phase support using exclusively progesterone. However, the rate of OHSS °III was increased after hCG administration in the high risk (4.8% *vs.* 2.5%) as well as in the low risk groups (2.6% *vs.* 1.6% and 1.4%), even if there was no statistically significant difference.

Finally, only patients in the group who received progesterone only in the high risk group had a significant trend towards less complaints during the end of the luteal phase (Fig. 2). Patients with three times hCG in the low risk group and once hCG additionally to vaginal progesterone in the high risk group instead of progesterone only, were those who had an increasing discomfort score over the whole luteal phase. However, this trend was not statistically significant. There was no difference between pregnant and non pregnant patients.

To conclude, the lower incidence of OHSS as well as the lower rate of complaints of patients who receive a luteal phase support without hCG administrations should reassure, to use vaginal progesterone whereever possible – especially, since there were no differences between the clinical ongoing pregnancy rates. If there are disadvantages of hCG for luteal phase support in patients with low estradiol levels, this must be further investigated in larger studies.

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