Human Reproduction, Vol. 15, (Suppl. 1), pp. 129–148, 2000

Progesterone for the luteal support of assisted reproductive technologies: clinical options

Cemal Posaci[1,2], Johan Smitz[1], Michel Camus[1], Kaan Osmanagaoglu[1] and Paul Devroey[1,3]

[1]Centre for Reproductive Medicine, Dutch-speaking Brussels Free University, Laarbeeklaan 101 B1090 Brussels, Belgium, and [2]Dokuz Eylul Universitesi Tip Fakultesi, Kadin Hastaliklari ve Dogum Anabilim Dali, Inciralti 35350 Izmir, Turkey

[3]To whom correspondence should be addressed

The role of progesterone in luteal support in assisted reproductive technologies (ART) is reviewed. There is insufficient data in ART treatment without gonadotrophin-releasing hormone (GnRH) analogues, to prove the necessity for luteal phase support using progesterone. Prospective studies have shown that ART cycles using GnRH analogues need to be supplemented. GnRH antagonists could have some adverse effects on the luteal phase. So far, no prospective randomized comparative study has been performed to investigate the necessity for luteal phase support when antagonists are used in ART cycles. Clinical outcome data (pregnancy and abortion rates) show similar success rates for human chorionic gonadotrophin (HCG) or progesterone supplementation. A major disadvantage of using HCG is the risk of maintaining or enhancing ovarian hyperstimulation syndrome. Of the several routes of administration of progesterone, the vaginal route is preferred because of its ease of use, reduced side-effects and, most importantly, the first uterine pass effect.

Key words: ART/luteal support/progesterone/route of administration

Introduction

It is generally believed that a decrease in the amount or the duration of progesterone secretion by the corpus luteum or the lack of an adequate response by the endometrium results in luteal phase deficiency (Jones, 1991; Ginsburg, 1992). A meta-analysis (Daya, 1988) was not able to show the necessity of progesterone supplementation for ovulation induction regimens without gonadotrophin-releasing hormone (GnRH) agonists in assisted reproductive technology (ART) cycles. Following the introduction of GnRH agonists in ART,

 © European Society of Human Reproduction and Embryology

Downloaded from https://academic.oup.com/humrep/article/15/suppl_1/129/716192 by Dokuz Eylul University Library (DEU) user on 02 September 2021

it has been clearly shown that the luteal phase is defective and needs to be supplemented (Smitz *et al.*, 1988; Smith *et al.*, 1989).

There are two possible means of luteal phase supplementation: (i) replacement therapy by exogenous progesterone; and (ii) administration of human chorionic gonadotrophin (HCG). The superiority of one drug over the other has been a subject of debate especially following the introduction of ART in infertility practice. There have been several comparative studies on HCG versus progesterone for luteal phase support. Although some studies have suggested luteal HCG supplementation as the treatment of choice in ART cycles using GnRH agonists (Buvat *et al.*, 1990; Golan *et al.*, 1993), others have not (Claman *et al.*, 1992; Araujo *et al.*, 1994). The use of HCG may be associated with an increased risk of ovarian hyperstimulation syndrome (OHSS) (Buvat *et al.*, 1990; Araujo *et al.*, 1994), and so routine use of HCG for luteal support should be avoided. In addition to the oral and i.m. route of progesterone, different modes of administration, e.g. nasal, subdermal, sublingual, rectal and vaginal routes, have recently been developed. The micronization procedure has improved the bioavailability of natural progesterone. The bioavailability of different forms of progesterone may fluctuate depending on their pharmaceutical preparation. In this paper, the role of progesterone in ART will be discussed with reference to current literature.

Pharmacodynamics

Different types of progesterone

Progesterone preparations can be divided into two main groups: natural progesterone and derivatives and synthetic progesterone and derivatives. Natural progesterone is quickly inactivated when taken orally because of its rapid metabolism in liver and intestine. Therefore, synthetic derivatives were developed to improve bioavailability.

There are two main groups of synthetic progestins: (i) the 17 hydroxyprogesterone derivatives and (ii) 19 nortestosterone derivatives (Table I). The latter comprise the 13-methyl gonanes group and 13 ethyl gonanes group. The change in the hormonal spectrum from androgenic to progestational activity is achieved by the removal of the angular methyl group in C19 (19-nor) and the introduction of the ethyl group in C17α (Kuhl, 1990).

Attempts to improve the bioavailibility of natural progesterone were investigated because of the limited therapeutic value of synthetic progestins due to side-effects and possible teratogenic effects (Hendrickx *et al.*, 1987b). For this reason, long-chain unsaturated fatty acids were used to improve oral progesterone absorption. Reduction of the particle size of progesterone by micronization enhances bioavailability (Maxson *et al.*, 1985; Hargrove *et al.*, 1989). However, the micronized form of a single oral dose is inefficient in providing adequate concentrations throughout the day (Nahoul *et al.*, 1987; Devroey *et al.*, 1989).

Downloaded from https://academic.oup.com/humrep/article/15/suppl_1/129/716192 by Dokuz Eylul University Library (DEU) user on 02 September 2021

Table I. Different types of progesterone and derivatives

Natural progesterone and derivatives
Progesterone
Dydroprogesterone
Medrogestone
Synthetic progesterone derivatives
17 hydroxyprogesterone derivatives
Hydroxyprogesterone heptanoate
Hydroxyprogesterone caproate
Chlormadinone acetate
Medroxyprogesterone acetate
Cyproterone acetate
19 nor testosterone derivatives
Norethisterone
Norethisterone acetate
Lynestrenol
Ethinodiol diacetate
Norgestrel
Levonorgestrel
Desogestrel
Norgestimate
Gestodene

Bioavailability

Following the intake of 100, 200 and 300 mg oral micronized progesterone in a fasting condition, the maximum plasma concentration (C_{max}) and maximum time for absorption (T_{max}) values were found to be 6.5 ± 1.8, 13.4 ± 3.6 and 32.3 ± 7.8 ng/ml after 2.7 ± 1.0, 2.7 ± 2.2 and 2.0 ± 1.4 h (mean ± SE) respectively (Table II). In addition, absorption of micronized progesterone was enhanced two-fold in the presence of food (Simón *et al.*, 1993). However, acceptable plasma progesterone concentrations were also obtained following a smaller dose of progesterone (i.e. 100 mg daily) administered via the vaginal mucosae. A maximum concentration of progesterone of 13.97 ng/ml can be reached within 3 h in the majority of cases following the administration of 100 mg micronized progesterone pervaginally (Archer *et al.*, 1995).

Plasma values have been found to be correlated with the doses of progesterone delivered by the vaginal route (Simón *et al.*, 1993), although some researchers did not observe significant differences of plasma progesterone values between the various doses administered by the vaginal route (Archer *et al.*, 1995). In a comparative study, the area under curve (AUC) values did not differ significantly between a daily dose of 200 mg orally and a 400 mg vaginal suppository (Norman *et al.*, 1991). In a study by Nahoul *et al.* (1993), plasma progesterone concentrations reached 4.7 ± 0.8 ng/ml by vaginal administration, but only 1.5 ± 0.2 (mean ± SE) by the oral route following 100 mg of a micronized progesterone intake in fasting condition.

Downloaded from https://academic.oup.com/humrep/article/15/suppl_1/129/716192 by Dokuz Eylul University Library (DEU) user on 02 September 2021

Table II. Some pharmacodynamic characteristics of the various routes of progesterone

Reference	Route of administration	Dose	C_{max} (ng/ml)	T_{max}	Time to return basal value
Nahoul *et al.*, 1987	Oral micronized (Utrogestan®)	200 mg/day	4.70 ± 1.15[b]	3 h	24 h
Devroey *et al.*, 1989	Oral micronized (Utrogestan®)	300 mg/day	7.21 ± 1.57[b]	2 h	6 h
	Vaginal micronized (Utrogestan®)	300 mg/day	8.83 ± 1.88[b]	2 h	8 h
	Vaginal micronized (Utrogestan®)	600 mg/day	13.09 ± 1.49[b]	4 h	8 h
	i.m. progesterone in oil	100 mg/day	71.87 ± 6.73[b]	2 h	10 h
Cicinelli *et al.*, 1991	Intranasal	11.2 mg/day	3.75 ± 0.21[a]	1 h	700 min
Norman *et al.*, 1991	Oral micronized (Utrogestan®)[c]	200 mg/day	28 ± 18.7[a]	3.1 h	24–32 h
	Vaginal suppository (Cyclogest®)	400 mg/day	29.2 ± 53.4[a]	8.1 h	24 h
Nahoul *et al.*, 1993	Oral micronized (Utrogestan®)[d]	100 mg/day	1.5 ± 0.2[b]	2 h	6 h
	Vaginal micronized (Utrogestan®)	100 mg/day	4.7 ± 0.8[b]	6 h	48 h
Simón *et al.*, 1993	Oral micronized (Utrogestan®)[c]	200 mg/day	69.2 ± 31[a]	3.1 ± 2.7 [i]	
	Oral micronized (Utrogestan®)[d]	100 mg/day	6.5 ± 1.8[a]	2.7 ± 1.0 [i]	
	Oral micronized (Utrogestan®)[d]	200 mg/day	13.4 ± 3.6[a]	2.7 ± 2.2 [i]	
	Oral micronized (Utrogestan®)[d]	300 mg/day	32.3 ± 7.8[a]	2.0 ± 1.4 [i]	
	Progesterone in oil	50 mg/day	14.3 ± 1.0[a]	8.7 ± 2.0 [i]	
Miles *et al.*, 1994	Vaginal micronized capsules	800 mg/day	6.64 ± 1.32[b]	4 h	
	i.m. progesterone in oil	100 mg/day	16.06 ± 1.63[b]	4 h	
Archer *et al.*, 1995	Vaginal suppository.	100 mg/day	14.50 ± 4.61[a]	3 h	
	Vaginal suppository	200 mg/day	14.69 ± 4.26[a]	8 h	
Cicinelli *et al.*, 1991	Vaginal micronized (Geston®)	100 mg/day	5.30 ± 1.04[a]	45 min	24 h
Fanchin *et al.*, 1997	Vaginal gel (Crinone®)	45 mg/every 2 days	3.90 ± 0.40[b]	7 h	37 h
	Vaginal gel (Crinone®)	90 mg/every 2 days	6.32 ± 1.30[b]	7h	43 h
	Vaginal gel (Crinone®)	180 mg/every 2 days	7.47 ± 0.61[b]	7 h	43 h

C_{max} = maximum plasma concentration; T_{max} = maximum time for absorption.
[a]Mean ± SD; [b]mean ± SE; [c]Non-fasting; [d]Fasting

Downloaded from https://academic.oup.com/humrep/article/15/suppl_1/129/716192 by Dokuz Eylul University Library (DEU) user on 02 September 2021

The plasma progesterone concentration returned to basal values within 6 h when the oral route was used, whereas progesterone values were still higher than the basal value at the end of 48 h when the vaginal route was used. There are more metabolites of progesterone in blood when using the oral route as a result of extensive metabolism in gut and liver (Nahoul *et al.*, 1993). Data show that bioavailability of progesterone is better when the vaginal route is used than when the oral one is used.

Progesterone i.m. in oil administration produces higher plasma concentrations which are sustained for longer periods. Bioavailability of oral progesterone is ~10% of i.m. progesterone (Simón *et al.*, 1993).

The bioavailability of progesterone administration by nasal spray has been shown (Cicinelli *et al.*, 1991). The progesterone administration yielded a mean C_{max} of 3.75 ng/ml at T_{max}: 1 h by nasal spray (Cicinelli *et al.*, 1991) (Table II) and a C_{max} of 14 ng/ml at T_{max} 2 h by rectal administration (Chakmakjian and Zachariah, 1987). The mean serum progesterone concentrations had been reported as 57.8 ng/ml in the patients undergoing cryopreserved embryo transfer given daily 1200 mg sublingual progesterone (Stovall *et al.*, 1996).

Route of administration

Various routes of administration were developed because of the relatively poor bioavailability and rapid inactivation of progesterone when administered orally. The various routes; i.m., vaginal, intranasal (Steege *et al.*, 1986; Cicinelli *et al.*, 1991), rectal (Chakmakjian and Zachariah, 1987) and sublingual (Stovall *et al.*, 1996), were all investigated. The transdermal route is not suitable for progesterone because of poor dermal absorption and a consequent requirement for high doses (de Ziegler *et al.*, 1995).

The vaginal route presents interesting advantages (Devroey *et al.*, 1989; Bourgain *et al.*, 1990; Smitz *et al.*, 1992a; Casanas-Roux *et al.*, 1996; Fanchin *et al.*, 1997). Micronized natural progesterone capsules formulated for oral use can be administered vaginally (Miles *et al.*, 1994).

Some of the advantages of the transvaginal route are: (i) avoidance of local pain; (ii) avoidance of first pass hepatic metabolism; (iii) rapid absorption; (iv) lack of undesirable side-effects, e.g. the hypnotic effect; (v) relatively high bioavailability; (vi) the possible reservoir effect of the vagina for a suppository; and (vii) most importantly a local endometrial effect (known as the uterine first pass effect).

Side-effects

The side-effects are more prominent with regard to the oral synthetic progestins. Of these, 19 norpregnane derivatives may have side-effects, e.g. masculinization, decreased high density lipoprotein concentrations (Larsson-Cohn *et al.*, 1981), luteolysis and possible teratogenic effects (Hendrickx *et al.*, 1987b) as a result of their androgenic properties, in addition to mood changes and depression.

Downloaded from https://academic.oup.com/humrep/article/15/suppl_1/129/716192 by Dokuz Eylul University Library (DEU) user on 02 September 2021

The major side-effects of oral micronized progesterone are sedative and hypnotic effects because the metabolites of progesterone effect the affinity of the γ-aminobutyric acid (GABA) receptor in the central nervous system (Arafat *et al.*, 1988). Other side-effects of oral micronized progesterone are fatigue, dizziness, headaches, faintness and urinary frequency (Norman *et al.*, 1991).

Local pain has been frequently reported when the i.m. route is used. Cold abscess may occur with the prolonged use of the i.m. route.

These side-effects occur seldom as a result of the vaginal route of administration. More specific for the vaginal route are vaginal irritation, vaginal discharge and dyspareunia. Pervaginally, progesterone can be administered in larger doses, e.g. 800 mg, without any reported side-effects (Miles, 1994).

Stovall *et al.* (1996) have not reported any side-effects in the patients undergoing cryopreserved embryo transfer following 1200 mg sublingual progesterone administration. Progesterone administration by nasal spray has not resulted in any nasal irritation (Cicinelli *et al.*, 1991).

Clinical use of progesterone in ART

Ovarian stimulation regimens without GnRH agonist cycles

The quality of the luteal phase after ovarian stimulation and the impact of follicle aspiration on the luteal phase have been investigated. Some authors have suggested that follicle aspiration may result in granulosa cell depletion leading to a negative effect on the luteal phase (Garcia *et al.*, 1981). Other studies, however, did not support this hypothesis (Kerin *et al.*, 1981; Frydman *et al.*, 1982). Whether the luteal phase must be supported in stimulated cycles without using GnRH agonists, remains an open question. Most studies have failed to demonstrate a clear benefit from luteal support in ART cycles with stimulation regimens, e.g. human menopausal gonadotrophin (HMG) either alone or combined with clomiphene citrate (CC) (Yovich *et al.*, 1985; Belaisch *et al.*, 1987; Daya 1988; Van Steirteghem *et al.*, 1988; Polson *et al.*, 1992).

In in-vitro fertilization (IVF) cycles using CC + HMG, there was no difference between the group with supplementation using 50 mg progesterone in oil (8%) and the group without supplementation (14%) in terms of pregnancy rate (Yovich *et al.*, 1985). Belaisch-Allart *et al.* (1987) investigated the effect of luteal supplementation with dydrogesterone on pregnancy rates in CC–HMG cycles. Although the pregnancy rates improved in the dydrogesterone group, the differences between the supplemented and the non-supplemented group were not statistically significant. Van Steirteghem *et al.* (1988) did not demonstrate any improvement on the basis of 50 mg progesterone i.m. in the patients treated by IVF or gamete intra-Fallopian transfer (GIFT) using CC–HMG cycles (26.4% in the supplemented group compared with 19% in the non-supplemented group).

Some authors have reported that ovulation induction protocols (which did not include GnRH agonist) had to be supported anyway in the luteal phase, because

Downloaded from https://academic.oup.com/humrep/article/15/suppl_1/129/716192 by Dokuz Eylul University Library (DEU) user on 02 September 2021

they observed an absolute fall in salivary and plasma progesterone concentrations (Nikkanen *et al.*, 1992). Plasma progesterone values were found to be higher following luteal HCG supplementation than following 50 mg daily progesterone administered vaginally in non-conception IVF cycles (Nikkanen *et al.*, 1992). Significantly higher pregnancy rates were found between a group supplemented with a 200 mg vaginal pessary and a non-supplemented group in GIFT cycles treated by HMG + CC (Polson *et al.*, 1992).

Triggering of ovulation by GnRH agonist instead of HCG may produce short luteal phase in the absence of hormonal luteal support (Corson *et al.*, 1993; Lanzone *et al.*, 1994). The luteal support by HCG administration overcomes luteal phase inadequacy after GnRH agonist-induced ovulation in gonadotrophin-stimulated cycles (Penarrubia *et al.*, 1998).

In the current literature there is insufficient evidence to recommend the routine use of progesterone to support the luteal phase after oocyte retrieval in ART cycles treated by CC–HMG or HMG alone (Daya, 1988).

GnRH agonist cycles

It was clearly shown that serum luteinizing hormone (LH) concentrations and the pituitary gonadotrophin reserve remain suppressed for at least 10 days after the ovulatory stimulus in GnRH agonist cycles (desensitization protocols). The premature luteal regression in GnRH agonist cycles may be (at least partly) attributed to prolonged desensitisation of the gonadotrophs by the agonist. For this reason, the use of luteal supplementation was advocated for GnRH agonist stimulated cycles (Smitz *et al.*, 1988).

Two prospective randomized studies (Smith *et al.*, 1989; Belaisch-Allart *et al.*, 1990) demonstrated the necessity for luteal support after GnRH agonist–HMG stimulation for IVF. Further studies to explain the underlying physiopathological mechanisms showed a reduction of the pituitary gonadotropin secretory capacity during the luteal phase in both long and short protocols (Smitz *et al.*, 1992b).

Luteal support by HCG significantly improved clinical and ongoing pregnancy rates as compared with oral micronized progesterone 400 mg, especially in short protocols with GnRH agonist and to a lesser degree in long ones (Buvat *et al.*, 1990). HCG supplementation was found to be superior to i.m. progesterone for the ultrashort protocol using GnRH agonist/HMG. In the study by Golan (1993) the conception rate was seven out of 30 using HCG and one out of 26 in i.m. progesterone groups, although the luteal progesterone concentrations were not significantly different. Other papers, however, reported similar pregnancy rates between groups using either HCG or progesterone given i.m. in IVF using a GnRH agonist (Smitz *et al.*, 1988; Claman *et al.*, 1992) (Table III).

Improved implantation and clinical pregnancy rates and lower abortion rates were seen in the 600 mg daily vaginal progesterone group as compared with the 50 mg daily i.m. progesterone group despite the lower serum progesterone concentration in the former (Smitz *et al.*, 1992a). There was no benefit from

Downloaded from https://academic.oup.com/humrep/article/15/suppl_1/129/716192 by Dokuz Eylul University Library (DEU) user on 02 September 2021

Table III. Pregnancy rates reported for various routes of luteal supplementation in IVF cycles with GnRH agonist

Reference	No. of cycles	Agonist protocol	Luteal support	Mid-luteal progesterone ng/ml	Implantation rate	Clinical pregnancy rate	Ongoing pregnancy rate	Abortion rate	Ectopic pregnancy rate
Smitz *et al.*, 1988	41	Buserelin long	HCG 3 × 2000 IU	150		31.7		30.7	
	50		Progesterone i.m. 50 mg + oestradiol valerate 6 mg/day	75		32	12.5		
Buvat *et al.*, 1990	70	Triptorelin long/short	HCG 3 × 1500 IU	114.4 ± 53.9[a]		31.4*	30*		
	70		Utrogestan 400 mg daily oral	86.6 ± 45[a]		14.2	11.4		
Claman *et al.*, 1992	72	Leuprolide long	HCG 3 × 1500 IU	123.3 ± 55[a]		18		23	–
	49	Progesterone i.m. 25 mg		115 ± 93*[a] pmol/l		12.2		14	28[c]
Smitz *et al.*, 1992a	131	Buserelin long	Progesterone i.m. 50 mg + oestradiol valerate 6 mg/day	98.8 ± 5.5[b]	11.6	26.7	19.1	29.4	
	131		Utrogestan vaginal 600 mg + oestradiol valerate 6 mg/day	69.9 ± 6.3*[b]	16.3	33.6	30.5	9.8*	
Smitz *et al.*, 1993	195	Buserelin long	Utrogestan vaginal 600 mg + oestradiol valerate 6 mg/day	90		29.2		14	1.7
	183		Utrogestan vaginal 600 mg	75		29.5		18.5	–
Araujo *et al.*, 1994	30	Leuprolide long	HCG 4 × 2000	150 ± 55[a]	12	36.7		0	
	34		Progesterone 50 mg i.m.	40 ± 30*[a]	14	35.3		16.6	
Pouly *et al.*, 1997	139	Decapeptyl long	Crinone 90 mg vaginal	29.9 ± 56.4[a]	35.3	28.8	25.9	10	12.5
	144		Utrogestan 300mg oral	50.9 ± 81.9*[a]	29.9	25	22.9	11.1	2.8

*Statistically significant ($P < 0.05$).
[a]Mean ± SD; [b]mean ± SE.
[c]Two out of seven pregnancies were ectopic.

Downloaded from https://academic.oup.com/humrep/article/15/suppl_1/129/716192 by Dokuz Eylul University Library (DEU) user on 02 September 2021

routinely supplementing GnRH agonist/HMG cycles with oestradiol valerate in addition to intravaginal micronized progesterone (Smitz *et al.*, 1993).

Van Steirteghem *et al.* (1988) reported similar pregnancy rates between the groups supplemented either by HCG or by progesterone i.m. in the IVF cycles stimulated with HMG + GnRH agonist. Clinical pregnancy and implantation rates were also similar between the two groups (HCG versus i.m. progesterone) (50 mg daily) although the serum oestradiol and progesterone concentrations on days 8–12 following transvaginal oocyte aspiration were higher in the HCG group (Araujo *et al.*, 1994).

In a prospective study, two different routes of luteal support were randomly allocated between two groups in IVF cycles previously down-regulated by Decapeptyl in a long protocol. In the first group, 90 mg Crinone was administered daily in a vaginal gel, in the second group 300 mg oral micronized progesterone (Utrogestan) was administered daily. The biochemical pregnancy rate per transfer, clinical pregnancy rate per transfer, delivery rate per transfer and newborn per transfer were surprisingly similar between the two groups (Pouly *et al.*, 1997) (Table III). This is the only study to report that the oral route was as effective as the vaginal one; the other publications had already reported that the vaginal route was superior to the oral one, since it improved the implantation rate (Smitz *et al.*, 1992a) and provided adequate endometrial response (Devroey *et al.*, 1989; Bourgain *et al.*, 1990, 1994; Critchley *et al.*, 1990; Casanas-Roux *et al.*, 1996).

Although the difference was not statistically significant, placental protein 14 (PP14) concentrations tended to be higher in patients supported with luteal HCG (Anthony *et al.*, 1993). The expression of integrin α_v is enhanced by HCG *in vitro* (Honda *et al.*, 1997). Relaxin is a luteal peptide hormone which has been shown to increase at the time of implantation and suggested to be regulated at least partially by HCG (Ghosh and Sengupta, 1998). Therefore, a potential advantage of HCG over progesterone is that HCG administration may be more physiological than progesterone because it may assist in stimulating the secretion of other factors important to endometrial maturation. One limitation of HCG is the risk of enhancing OHSS. When the oestradiol concentration is >2700 pg/ml (Buvat *et al.*, 1990) or the number of follicles is >10 (Araujo *et al.*, 1994), luteal support with HCG should be avoided.

There are still a lot of unanswered questions with regard to progesterone supplementation. When should progesterone supplementation be initiated for luteal support? How long must treatment be continued?

Progesterone supplementation may be started on the day after the ovulatory HCG dose (Smitz *et al.*, 1992a), on the day after oocyte recovery (Buvat *et al.*, 1990) or on the day of embryo transfer (Claman *et al.*, 1992; Araujo *et al.*, 1994; Pouly *et al.*, 1997). The patient should continue to take progesterone for at least 12–14 days until possible menses.

If the pregnancy test is found to be positive, progesterone supplementation may be continued up to 30 days after the embryo transfer (Araujo *et al.*, 1994; Pouly *et al.*, 1997), until fetal heart activity is seen (Claman *et al.*, 1992) or until the 12th week of gestation (Smitz *et al.*, 1992a).

Downloaded from https://academic.oup.com/humrep/article/15/suppl_1/129/716192 by Dokuz Eylul University Library (DEU) user on 02 September 2021

Some reports have shown an increased pregnancy rate among women with higher concentrations of progesterone during the very early luteal phase (Lenton *et al.*, 1982; Garcia *et al.*, 1984; Yovich *et al.*, 1985). These suggest the possibility of increasing pregnancy rates by giving progesterone in the peri-ovulatory and the early luteal phases.

Progesterone i.m. supplementation (25 mg given 21 h after HCG, 50 mg 35 h after HCG and 50 mg 60 h after HCG) and HCG (a second injection of 5000 IU 24 h after the initial HCG) around the time of oocyte recovery in the IVF cycles stimulated with CC + HMG failed to affect pregnancy rate, compared with a control group (Trounson *et al.*, 1986). Supplementation of the luteal phase from days 7–16 with i.m. injections of 50 mg of progesterone daily had no significant effect on improving pregnancy rates in a controlled trial reported by Leeton *et al.* (1985). However, in agonist-induced ovulation cycles, administration of 100 mg progesterone i.m. per day beginning on the day of HCG for 6 days may improve the pregnancy rate (41.2 versus 23.3%) (Ben-Nun *et al.*, 1990). In addition, endometrial biopsies taken 48 h after ovum retrieval in patients with no fertilization revealed mostly advanced endometrial dating in relation to the day of HCG.

A meta-analysis reported that the luteal phase must be supported by HCG rather than progesterone in IVF cycles using GnRH agonist (Soliman *et al.*, 1994). However, most of the studies included in this meta-analysis had cycles supplemented with progesterone i.m.

The relatively low concentrations of luteal progesterone in the groups supplemented with progesterone i.m. versus HCG (Nader *et al.*, 1988; Claman *et al.*, 1992; Araujo *et al.*, 1994) may be attributed to two causes: a stimulatory effect by HCG on the corpus luteum and a suppressive effect by exogenously administered progesterone on the concentration of plasma LH during the luteal phase. The former probably plays a more important role. HCG in itself may also have a negative effect on pituitary LH secretion (Mores *et al.*, 1996).

The question of what the minimal mid-luteal plasma concentration of progesterone is that will ensure an adequate luteal phase in ovulation induction cycles, is still unanswered. 10 ng/ml is considered to be the lowest value for an adequate luteal phase in natural cycles (Jordan *et al.*, 1994).

There is still a substantial lack of data to compare the effect of different plasma concentrations of progesterone on the endometrium and to find cut-off concentrations of plasma progesterone for an adequate luteal phase in stimulated cycles. No data are yet available which have focused on finding a cut-off value for progesterone concentrations in view of implantation and pregnancy rates.

What is the optimal dose of progesterone for a high pregnancy rate? There is no single optimal dose, since there are different routes of administration. On the basis of prospective comparative studies and observations on the morphology of endometrial biopsies, we propose that optimal doses of progesterone for different routes of administration are $3\times100/3\times200$ mg for the vaginal route and 2×50 mg daily for the i.m. route. For ovarian ovulation induction, the oral route of administration is inadequate.

Downloaded from https://academic.oup.com/humrep/article/15/suppl_1/129/716192 by Dokuz Eylul University Library (DEU) user on 02 September 2021

GnRH antagonists and the luteal phase

The advantages of GnRH antagonists can be summarized as follows: immediate arrest of gonadotrophin secretion, shorter time of administration and successful LH suppression (Albano *et al.*, 1997). The effects of antagonists on the luteal phase of ovulation induction is still unknown. Although the luteal phase has been reported normal in terms of length and progesterone concentrations in the antagonist cycle in normal women (Ditkoff *et al.*, 1991), there has been no prospective double-blind comparative study to show whether or not the luteal phase should be supported in the ART cycles using antagonists.

A direct inhibitory effect by GnRH antagonist (Nal-Lys antagonist: antide; Contraceptive Development Branch, NIH, Betheseda, MD, USA) on basal progesterone and pregnenolone production had been shown in the luteal cells obtained from day 8 pregnant rats (Srivastava *et al.*, 1994). A profound suppression of LH concentrations was found during the luteal phase in the ART cycles using antagonist. Mid-luteal progesterone concentrations were found to be 209.41 ± 76.34 ng/ml (Felberbaum *et al.*, 1996) and 150 ng/ml (Diedrich *et al.*, 1994) in ART cycles using 3 mg Cetrorelix (Astra Medical, Frankfurt, Germany) and supporting the luteal phase with HCG. On the other hand, a study including five women who had undergone ovarian stimulation using CC + HMG + antagonist (Nal-Glu) showed that progesterone went up to maximum concentrations of 50.3 ± 12.8 ng/ml (mean ± SD) on day 6 after HCG administration without any luteal support. This suggested the absence of a negative effect from Nal-Glu on the early luteal phase (Frydman *et al.*, 1991).

The presence of vaginal bleeding and low serum oestradiol and progesterone concentrations in the mid-luteal phase may be attributed to lack of luteal support in the ART cycles using antagonist (Albano *et al.*, 1996, 1997). Low luteal LH concentrations were found in the ART cycles using antagonist and supported with HCG. The low concentrations of serum LH in the luteal phase were probably due to suppression by increased oestradiol and progesterone after ovulation stimulation (Diedrich *et al.*, 1994).

Clinical pregnancies/cycle and clinical pregnancies/transfer rates were found to be 36.4 and 30.0% respectively in 11 women undergoing IVF with Cetrorelix + 300 mg daily micronized progesterone (Utrogestan®; Besins Iscovesco Pharmaceutical, Paris, France) (Olivennes *et al.*, 1995); equivalent figures were 34.5 and 29% in 69 women undergoing IVF or intracytoplasmic sperm injection (ICSI), treated with Cetrorelix + luteal HCG (Albano *et al.*, 1997).

There is one single report showing that antagonists have no deleterious effect on the luteal phase in spontaneous cycles (Ditkoff *et al.*, 1991). Recently it has been reported that the duration of the luteal phase was <12 days in three of the six patients undergoing ovarian stimulation with HMG + Cetrorelix without any luteal support (Albano *et al.*, 1998). However, for patients in whom ovulation was stimulated and who had previously been treated by an antagonist, there has been no double-blind controlled study to investigate the differences between a supplemented and a non-supplemented luteal phase. Development of endometrial

Downloaded from https://academic.oup.com/humrep/article/15/suppl_1/129/716192 by Dokuz Eylul University Library (DEU) user on 02 September 2021

receptivity and implantation potential in cycles stimulated with GnRH antagonist has yet to be investigated. Perhaps the association of HMG/follicle stimulating hormone, and antagonist and HCG is responsible for a luteal phase defect? Further investigations are needed.

Endometrial development after luteal supplementation

An adequate luteal phase results from at least two essential components: firstly an adequate corpus luteum function and secondly an adequate endometrial response to progesterone.

Pinopodes are specialized bulging surface membranes. They are progesterone-dependent cellular organelles appearing for only 2 or 3 days between days 19 and 21 of the normal menstrual cycle. Pinopodes, although not clearly defined, are thought to be related to the implantation window (Beier and Beier-Hellwig, 1998). A human ex-vivo perfusion model was developed using hysterectomy specimens removed with a rim of 1.5–2 cm vaginal tissue. It was shown that radioactive progesterone applied to the vaginal cuff progressively migrates into the uterus and high concentrations are reached in both the endometrium and the myometrium (Bulletti *et al.*, 1997a). Endometrial accumulation of progesterone was higher in the luteal phase than in the proliferative phase. The higher accumulation of progesterone during the luteal phase might be attributed to two causes: the higher concentration of progesterone receptors in the early luteal phase and the existence of different patterns of uterine contractions during the menstrual cycle (Bulletti *et al.*, 1993, 1997b). The homogeneous distribution of progesterone throughout the endometrium suggests a local endometrial effect: this local effect is called the uterine first pass effect (Bulletti *et al.*, 1997a).

Miles *et al.* (1994) compared the effects of progesterone administered intravaginally (800 mg daily micronized progesterone) with progesterone administered i.m. (100 mg daily) on endometrial progesterone concentrations and endometrial morphology in agonadal patients. They demonstrated that endometrial progesterone concentrations were significantly higher via the vaginal route despite the lower plasma concentrations (Miles *et al.*, 1994). Histological endometrial data were similar between the vaginal and the i.m. groups. However, a slight maturation delay in the glandular component was present after i.m. therapy.

Development of endometrial receptivity, which is essential for patients without ovaries, can be obtained by means of vaginal progesterone in donor oocyte programmes (Devroey *et al.*, 1989; Bourgain *et al.*, 1990). In a group of patients without ovaries, endometrial morphology was investigated according to three different treatment regimes: i.m. progesterone (50 mg), oral Utrogestan (300 mg) or intravaginal Utrogestan (300–600 mg). After vaginal application of micronized progesterone, endometrial morphology closely matched that of the natural cycle while the endometrium was heterogeneous or inadequate in both i.m. and oral groups (Devroey, 1989).

Critchley *et al.* (1990) investigated the effects of progesterone administered either vaginally or orally on the endometrial morphology of women with

Downloaded from https://academic.oup.com/humrep/article/15/suppl_1/129/716192 by Dokuz Eylul University Library (DEU) user on 02 September 2021

premature ovarian failure. They demonstrated that endometrial morphology most closely resembled that of the natural cycle as a result of the vaginal route of supplementation and that histological appearance was invariably abnormal as a result of the oral route (Critchley *et al.*, 1990). Transvaginal or i.m. progesterone administration provides optimal endometrial receptivity in oocyte donation programmes (de Ziegler *et al.*, 1994).

Recently, a new progesterone vaginal gel has been developed (Crinone®; Ares-Serono International, S.A., Switzerland). Women without ovarian function received natural progesterone gel (Crinone) transvaginally in various doses of 45, 90 or 180 mg every other day following oestrogen (Fanchin *et al.*, 1997). Histopathological evaluation revealed that secretory transformation was observed in all subjects (Fanchin *et al.*, 1997). The efficacy of a vaginal progesterone preparation (Crinone, 180 mg daily) with progesterone i.m. (100 mg daily) was investigated in a prospective randomized study within a donor oocyte programme (Gibbons *et al.*, 1998). Endometrial histology was in-phase for all the subjects in both groups. Although the women supplemented with intravaginal progesterone had higher implantation and ongoing pregnancy rates than the women supplemented with i.m. progesterone, the differences were not statistically significant (Gibbons *et al.*, 1998). Sublingual progesterone administration in high doses (1200 mg daily) may be an alternative to the vaginal or i.m. route (Stovall *et al.*, 1996).

In a comparative study (Bourgain *et al.*, 1994) different types of luteal support were investigated: 3×1500 IU HCG (on days 4, 8 and 12 after the ovulatory HCG dose), 100 mg i.m. progesterone daily or a vaginal 600 mg daily with or without oestradiol valerate were administered to patients previously undergoing ovulation stimulation with a combined GnRH agonist + HMG regime. Endometrial sampling showed that the tissues most homogeneously developed and most frequently in phase were those resulting from progesterone being administered by the intravaginal route (Bourgain *et al.*, 1994). When the same observer analysed the endometria from patients supplemented with i.m. progesterone or HCG, there was an increased frequency of dissociated development between glands and stroma and a maturation delay. There were no arguments from morphological appearance to suggest an effect from an additional oestradiol (Progynova®; Schening, Berlin, Germany) supplementation on endometrium.

Secretory transformation of endometrium was obtained in all post-menopausal women treated by oestrogen + natural vaginal progesterone gel (Crinone), even though this progesterone was used in low doses, e.g. 45 mg progesterone every other day (Casanas-Roux *et al.*, 1996) (Table IV). The endometrium from menopausal women was found to be in phase despite very low plasma progesterone concentrations in 90% of the women treated by oestrogen + Crinone (Table IV). Of the patients, 10% showed a slight maturation delay. Clinical observation also suggested the presence of a local endometrial effect from progesterone when administered intravaginally. When an i.m. form of progesterone (progesterone in oil) was administered vaginally, serum concentration appeared to be low, although

Downloaded from https://academic.oup.com/humrep/article/15/suppl_1/129/716192 by Dokuz Eylul University Library (DEU) user on 02 September 2021

Table IV. The effect of various routes of progesterone on the endometrium in women with non-functioning ovaries

Reference	Subjects (*n*)	Type of Progesterone	Plasma value (ng/ml)	Secretory endometrium	Endometrial dating
Devroey *et al.*, 1989	18	300 mg vaginal daily[c]	8.3 ± 1.2	18/18	18/18 in phase
(Patients without ovaries)	10	600 mg vaginal daily[c]	11.1 ± 1.1	10/10	10/10 in phase
	16	300 mg oral daily[c]	3.26 ± 0.62		No evidence of adequate progesterone effect
	31	100mg in oil (i.m.) daily	43.9 ± 1.9	31/31	2/31 out of phase
Bourgain *et al.*, 1990	12	300 mg oral daily[c]	2.8 ± 0.6[b]		Never corresponded to the expected cycle day
(Patients without ovaries)	21	300 mg vaginal daily[c]	6.8 ± 1.3[b]		All specimens had mature endometria
	8	600 mg vaginal daily[c]	8.1 ± 1.7[b]		All specimens had mature endometria
	34	100 mg in oil (i.m.) daily	43.4 ± 0.6[b]		47.5% of specimens corresponded the expected cycle day, 43.5% had delayed maturation, 9% the glandular and the stromal development did not correspond to the same cycle day
Critchley *et al.*, 1990	10	300 mg oral daily[d]	4.7 ± 0.7[b]		Four out of five biopsies invariably revealed very abnormal appearance
(Patients with premature ovarian failure)	10	300 mg vaginal daily[d]	15 ± 1.7[b]		Five out of six biopsies revealed physiological appearance
de Ziegler *et al.*, 1992	22	300 mg vaginal daily[c]		22/22	1/22 out of phase
(Patients without ovaries)					
Miles *et al.*, 1994	15	800 mg vaginal daily[d]	11.9 ± 1.2[b]	15/15	15/15 in phase
(Functionally agonadal women)	5	100 mg in oil (i.m.) daily	69.8 ± 5.9[b]	5/5	5/5 in phase. A slight maturation delay in the glandular component commonly was present
Casanas-Roux *et al.*, 1996	10	45 mg/every other day[e]	2.9 ± 1.2[a]	20/20	18/20 in phase
(Menopausal women)	10	90 mg/every other day[e]	3.9 ± 1.8[a]	20/20	18/20 in phase
Fanchin *et al.*, 1997	14	45 mg/every other day[e]	2.4 ± 0.2[b]	20/20	All biopsies taken by day 20 corresponded with day 18
(Functionally agonadal women)	13	90 mg/every other day[e]	3.6 ± 0.2[b]	20/20	All biopsies taken by day 20 corresponded with day 18
	13	180 mg/every other day[e]	3.4 ± 0.4[b]	20/20	All biopsies taken by day 20 corresponded with day 18
Ross *et al.*, 1997	31	45 mg/every other day[e]	4.6 ± 0.8[b]	15/19	No data available
(Menopausal women)	31	90 mg/every other day[e]	6.8 ± 1.2[b]	20/22	No data available
Gibbons *et al.*, 1998	54	180 mg/every other day[e]	19	55/55	55/55 in phase
(Premature ovarian failure)	18	100 mg in oil (i.m.) daily	89.3	23/23	23/23 in phase

[a]Mean ± SD; [b]mean ± SE; [c]micronized progesterone (Utrogestan®); [d]micronized progesterone; [e]progesterone vaginal gel (Crinone®).

Downloaded from https://academic.oup.com/humrep/article/15/suppl_1/129/716192 by Dokuz Eylul University Library (DEU) user on 02 September 2021

secretory transformation occurred in all menopausal women who had previously taken oestrogen (Cicinelli *et al.*, 1996).

Natural progesterone gel (45 mg every other day), administered vaginally is capable of transforming endometrium into the secreting phase in post-menopausal women who have previously been exposed to oestrogen. However, orally administered progesterone in a daily dose of 300 mg did not give rise to a secretory endometrial transformation (Bourgain, 1990; Critchley, 1990). de Ziegler *et al.* (1992) reported 21 out of 22 in-phase endometria in patients with no ovaries or with inactive ovaries following a combination of oestrogen treatment with 300 mg daily transvaginal micronized progesterone.

Safety

After the administration of medroxyprogesterone, cleft palate deformities in rabbits (Andrew and Staples, 1977) appeared and an increase in left palate deformities and urinary abnormalities was shown in mice treated by cyproterone acetate (Eibs *et al.*, 1982).

However, clinical studies in humans have shown that the association of progesterone intake during pregnancy and cardiac malformation (odds ratio: 1.5) (Rothman *et al.*, 1979), or oesophageal atresia (odds ratio: 2.87) (Lammer and Cordero, 1986) is poor and the absolute risk is low. In a study including 382 women exposed previously to progesterone vaginal suppositories and/or i.m. 17 hydroxyprogesterone, one club foot and cleft palate, one hydrocephaly, one transposition of great vessels, one ventricular septal defect and pulmonary stenosis, one Sprengle's deformity and omphalocele were reported and it was concluded that progesterone administration did not increase fetal abnormalities (Check *et al.*, 1986).

No teratogenic effects from hydroxyprogesterone caproate have been shown in rhesus and cynomolgus monkeys at doses which were 10–70 times higher than in human therapeutic use (Hendrickx *et al.*, 1987a; Carbone and Brent, 1993). When norethisterone acetate was administered to monkeys at dosages up to 1000 times the human dose equivalent from days 20–50 of pregnancy, some virilization occurred in fetuses but there was no extragenital teratogenicity (Hendrickx *et al.*, 1987b). Furthermore, in-vitro study has shown that prenatal exposure of the developing human female genital tract to progesterone is not associated with any obvious teratogenic effect (Cunha *et al.,* 1988).

Case controlled studies including a large number of cases have shown that *in utero* exogenous progestin exposure did not influence fetal outcome (Resseguie *et al.*, 1985, Martinez-Frias *et al.*, 1998).

In 1973 a high frequency of exposure to female sex hormones had been reported among the mothers of 10 infants with the VACTERL (vertebra, anal, cardiac, tracheoesephageal, renal, limb deformity) association (Nora and Nora, 1973). They reported that 43% of mothers of infants with the VACTERL association recalled use of a sex hormone in the first trimester, compared with 8% exposure among the control mothers and they found that the relative risk

Downloaded from https://academic.oup.com/humrep/article/15/suppl_1/129/716192 by Dokuz Eylul University Library (DEU) user on 02 September 2021

was 8.41. The same author later reported the relative risk as 5.58 and 3.35 in two case-controlled studies involving maternal hormonal exposure and patients with congenital heart lesions without other malformations (Nora and Nora, 1978). However, 8 years later it was reported that the frequency of sex hormone use among mothers of infants with VACTERL association was nearly identical to that of controls (odds ratio: 0.98) (Lammer *et al.*, 1986).

The vast majority of epidemiological studies do not indicate teratogenic effects from natural progesterone. The 19 nor-testosterone derivatives had some androgenic effects on fetuses. Natural micronized progesterone which is commonly used for luteal support is probably safe for the fetus. However, prospective double-blind studies with large series are necessary.

References

Albano, C., Smitz, J., Camus, M. *et al.* (1996) Hormonal profile during the follicular phase in cycles stimulated with a combination of human menopausal gonadotrophin and gonadotrophin-releasing hormone antagonist (Cetrorelix). *Hum. Reprod.*, **11**, 2114–2118.

Albano, C., Smitz, J., Camus, M. *et al.* (1997) Comparison of different doses of gonadotropin-releasing hormone antagonist Cetrorelix during controlled ovarian hyperstimulation. *Fertil. Steril.*, **67**, 917–922.

Albano, C., Grimbizis, G., Smitz, J. *et al.* (1998) The luteal phase of nonsupplemented cycles after ovarian superovulation with human menopausal gonadotropin and the gonadotropin-releasing hormone antagonist Cetrorelix. *Fertil. Steril.*, **70**, 357–359.

Andrew, F.D. and Staples, R.E. (1977) Prenatal toxicity of medroxyprogesterone acetate in rabbits, rats, and mice. *Teratology*, **15**, 25–32.

Anthony, F.W., Smith, E.M., Gadd, S.C, *et al.* (1993) Placental protein 14 secretion during *in vitro* fertilization cycles with and without human chorionic gonadotropin for luteal support. *Fertil. Steril.*, **59**, 187–191.

Arafat, E.S., Hargrove, J.T., Maxson, W.S. *et al.* (1988) Sedative and hypnotic effects of oral administration of micronized progesterone may be mediated through its metabolites. *Am. J. Obstet. Gynecol.*, **159**, 1203–1209.

Araujo, E. Jr, Bernardini, L., Frederick, J.L. *et al.* (1994) Prospective randomized comparison of human chorionic gonadotropin versus intramuscular progesterone for luteal-phase support in assisted reproduction. *J. Assist. Reprod. Genet.*, **11**, 74–78.

Archer, D.F., Fahy, G.E., Viniegra-Sibal, A. *et al.* (1995) Initial and steady-state pharmacokinetics of a vaginally administered formulation of progesterone. *Am. J. Obstet. Gynecol.*, **173**, 471–477.

Beier, H.M. and Beier-Hellwig, K. (1998) Molecular and cellular aspects of endometrial receptivity. *Hum. Reprod. Update*, **4**, 448–458.

Ben-Nun, I., Ghetler, Y., Jaffe, R. *et al.* (1990) Effect of preovulatory progesterone administration on the endometrial maturation and implantation rate after *in vitro* fertilization and embryo transfer. *Fertil. Steril.*, **53**, 276–281.

Belaisch-Allart, J., Testart, J, Fries, N. *et al.* (1987) The effect of dydrogesterone supplementation in an IVF programme. *Hum. Reprod.*, **2**, 183–185.

Belaisch-Allart, J., De Mouzon, J., Lapousterle, C. *et al.* (1990) The effect of HCG supplementation after combined GnRH agonist/HMG treatment in an IVF programme. *Hum. Reprod.*, **5**, 163–166.

Bourgain, C., Devroey, P., Van Waesberghe, L. *et al.* (1990) Effects of natural progesterone on the morphology of the endometrium in patients with primary ovarian failure. *Hum. Reprod.*, **5**, 537–543.

Bourgain, C., Smitz, J., Camus, M. *et al.* (1994) Human endometrial maturation is markedly improved after luteal supplementation of gonadotrophin-releasing hormone analogue/human menopausal gonadotrophin-stimulated cycles. *Hum. Reprod.*, **9**, 32–40.

Downloaded from https://academic.oup.com/humrep/article/15/suppl_1/129/716192 by Dokuz Eylul University Library (DEU) user on 02 September 2021

Bulletti, C., Prefetto, R.A., Bazzocchi, G. *et al.* (1993) Electromechanical activities of human uteri during extra-corporeal perfusion with ovarian steroids. *Hum. Reprod.*, **8**, 1558–1563.

Bulletti, C., de Ziegler, D., Flamigni, C. *et al.* (1997a) Targeted drug delivery in gynaecology: the first uterine pass effect. *Hum. Reprod.*, **12**, 1073–1079.

Bulletti, C., de Ziegler, D., Giacomucci, E. *et al.* (1997b) Vaginal drug delivery: the first uterine pass effect. *Ann. N.Y. Acad. Sci.*, **26**, 285–290.

Buvat, J., Marcolin, G., Guittard, C. *et al.* (1990) Luteal support after luteinizing hormone-releasing hormone agonist for *in vitro* fertilization: superiority of human chorionic gonadotropin over oral progesterone. *Fertil. Steril.*, **53**, 490–494.

Carbone, J.P., Brent, R.L. (1993) Genital and nongenital teratogenesis of prenatal progestogen therapy: the effects of 17 alpha-hydroxyprogesterone caproate on embryonic and fetal development and endochondral ossification in the C57B1/6J mouse. *Am. J. Obstet. Gynecol.*, **169**, 1292–1298.

Casanas-Roux, F.C., Nisolle, M., Marbaix, E (1996) Morphometric, immunohistological and three-dimensional evaluation of the endometrium of menopausal women treated by oestrogen + Crinone, a new slow-release vaginal progesterone. *Hum. Reprod.*, **11**, 357–363.

Chakmakjian, Z.H. and Zachariah, N.Y. (1987) Bioavailability of progesterone with different modes of administration. *J. Reprod. Med.*, **32**, 443–448.

Check, J.H., Rankin, A. and Teichman, M. (1986) The risk of fetal anomalies as a result of progesterone therapy during pregnancy. *Fertil. Steril.*, **45**, 575–577.

Cicinelli, E., Fanelli, F., Ragno, G. *et al.* (1991) Progesterone administration by nasal spray. *Fertil. Steril.*, **56**, 139–141.

Claman, P., Domingo, M. and Leader, A. (1992) Luteal phase support in in-vitro fertilization using gonadotrophin releasing hormone analogue before ovarian stimulation: a prospective randomized study of human chorionic gonadotrophin versus i.m. progesterone. *Hum. Reprod.*, **7**, 487–489.

Corson, S.L., Batzer, F.R., Gocial, B. *et al.* (1993) The luteal phase after ovulation induction with human menopausal gonadotropin and one versus two doses of a gonadotropin-releasing hormone agonist. *Fertil. Steril.*, **59**, 1251–6.

Critchley, H.O., Buckley, C.H. and Anderson, D.C. (1990) Experience with a 'physiological' steroid replacement regimen for the establishment of a receptive endometrium in women with premature ovarian failure. *Br. J. Obstet. Gynaecol.*, **97**, 804–810.

Cunha, G.R., Taguchi, O., Sugimura, Y. *et al.* (1988) Absence of teratogenic effects of progesterone on the developing genital tract of the human female fetus. *Hum. Pathol.*, **19**, 77–783.

Daya, S. (1988) Efficacy of progesterone support in the luteal phase following in-vitro fertilization and embryo transfer: meta-analysis of clinical trials. *Hum. Reprod.*, **3**, 731–734.

Devroey, P, Palermo, G, Bourgain, C. *et al.* (1989) Progesterone administration in patients with absent ovaries. *Int. J. Fertil.*, **34**, 188–193.

de Ziegler, D., Bergeron, C., Cornel, C. *et al.* (1992) Effects of luteal estradiol on the secretory transformation of human endometrium and plasma gonadotropins. *J. Clin. Endocrinol. Metab.*, **74**, 322–331.

de Ziegler, D., Fanchin, R., Massonneau, M. *et al.* (1994) Hormonal control of endometrial receptivity. The egg donation model and controlled ovarian hyperstimulation. *Ann. N.Y. Acad. Sci.*, **30**, 209–220.

de Ziegler, D., Seidler, L., Scharer, E. *et al.* (1995) Administration non orale de la progestérone: expériences et avenir de la voie transvaginale. *Schweiz Rundsch. Med. Prax.*, **84**, 127–133.

Diedrich, K., Diedrich, C., Santos, E. *et al.* (1994) Suppression of the endogenous luteinizing hormone surge by the gonadotrophin-releasing hormone antagonist Cetrorelix during ovarian stimulation. *Hum. Reprod.*, **9**, 788–791.

Ditkoff, E.C., Cassidenti, D.L., Paulson, R.J. *et al.* (1991) The gonadotropin-releasing hormone antagonist (Nal-Glu) acutely blocks the luteinizing hormone surge but allows for resumption of folliculogenesis in normal women. *Am. J. Obstet. Gynecol.*, **165**, 1811–1817.

Eibs, H.G., Spielmann, H., Hagele, M. (1982) Teratogenic effects of cyproterone acetate and medroxyprogesterone treatment during the pre- and postimplantation period of mouse embryos. I. *Teratology*, **25**, 27–36.

Fanchin, R., de Ziegler, D., Bergeron, C. *et al.* (1997) Transvaginal administration of progesterone : Dose-response data support a first uterine pass effect. *Obstet. Gynecol.*, **90**, 396–401.

Downloaded from https://academic.oup.com/humrep/article/15/suppl_1/129/716192 by Dokuz Eylul University Library (DEU) user on 02 September 2021

Felberbaum, R., Reissmann, T., Kupker, W. *et al.* (1996) Hormone profiles under ovarian stimulation with human menopausal gonadotropin (hMG) and concomitant administration of the gonadotropin-releasing hormone (GnRH)-antagonist Cetrorelix at different dosages. *J. Assist. Reprod. Genet.*, **13**, 216–222.

Frydman, R., Testart, J., Giacomini, P. *et al.* (1982) Hormonal and histological study of the luteal phase in women following aspiration of the preovulatory follicle. *Fertil. Steril.*, **38**, 312–317.

Frydman, R., Cornel, C., de Ziegler, D. *et al.* (1991) Prevention of premature luteinizing hormone and progesterone rise with a gonadotropin-releasing hormone antagonist, Nal-Glu, in controlled ovarian hyperstimulation. *Fertil. Steril.*, **56**, 923–927.

Garcia, J., Jones, G.S., Acosta, A.A. *et al.* (1981) Corpus luteum function after follicle aspiration for oocyte retrieval. *Fertil. Steril.*, **36**, 565–572.

Garcia, J.E., Acosta, A.A., Hsiu, J.G. *et al.* (1984) Advanced endometrial maturation after ovulation induction with human menopausal gonadotropin/human chorionic gonadotropin for *in vitro* fertilization. *Fertil. Steril.*, **41**, 31–35.

Ghosh, D. and Sengupta, J. (1998) Recent developments in endocrinology and paracrinology of blastocyst implantation in the primate. *Hum. Reprod. Update*, **4**, 153–68.

Gibbons, W.E., Toner, J.P., Hamacher, P. *et al.* (1998) Experience with a novel vaginal progesterone preparation in a donor oocyte program. *Fertil. Steril.*, **69**, 96–101.

Ginsburg, K.A. (1992) Luteal phase defect. Etiology, diagnosis, and management. *Endocrinol. Metab. Clin. N. Am.*, **21**, 85–104.

Golan, A., Herman, A., Soffer, Y. *et al.* (1993) Human chorionic gonadotrophin is a better luteal support than progesterone in ultrashort gonadotrophin-releasing hormone agonist/menotrophin in-vitro fertilization cycles. *Hum. Reprod.*, **8**, 1372–1375.

Hargove, J.T., Maxson, W.A. and Wentz, A.C. (1989) Absorption of oral progesterone is influenced by vehicle and particle size. *Am. J. Obstet. Gynecol.*, **161**, 948–951.

Hendrickx, A.G., Korte, R., Leuschner, F. *et al.* (1987a) Embryotoxicity of sex steroidal hormones in nonhuman primates: II. Hydroxyprogesterone caproate, estradiol valerate. *Teratology*, **35**, 129–136.

Hendrickx, A.G., Korte, R., Leuschner, F. *et al.* (1987b) Embryotoxicity of sex steroidal hormone combinations in nonhuman primates: I. Norethisterone acetate + ethinylestradiol and progesterone + estradiol benzoate (*Macaca mulatta*, *Macaca fascicularis*, and *Papio cynocephalus*). *Teratology*, **35**, 119–127.

Honda, T., Fujiwara, H., Yamada, S., *et al.* (1997) Integrin α_v is expressed on human luteinizing granulosa cells during corpus luteum formation, and its expression is enhanced by human chorionic gonadotrophin *in vitro*. *Mol. Hum. Reprod.*, **3**, 979–84.

Jones, G.S. (1991) Luteal phase defect: a review of pathophysiology. *Curr. Opin. Obstet. Gynecol.*, **3**, 641–648.

Jordan, J., Craig, K., Clifton, D.K. *et al.* (1994) Luteal phase defect: the sensitivity and specificity of diagnostic methods in common clinical use. *Fertil. Steril.*, **62**, 54–62.

Kerin, J.F., Broom, T.J., Ralph, M.M. *et al.* (1981) Human luteal phase function following oocyte aspiration from the immediately preovular graafian follicle of spontaneous ovular cycles. *Br. J. Obstet. Gynaecol.*, **88**, 1021–1028.

Kuhl, H. (1990) Pharmacokinetics of oestrogens and progestogens. *Maturitas*, **12**, 171–197.

Lammer, E.J., Cordero, J.F. (1986) Exogenous sex hormone exposure and the risk for major malformations. *J. Am. Med. Assoc.*, **13**, 3128–3132.

Lammer, E.J., Cordero, J.F. and Khoury, M.J. (1986) Exogenous sex hormone exposure and the risk for VACTERL association. *Teratology*, **34**, 165–169.

Lanzone, A., Fulghesu, A.M., Villa, P. *et al.* (1994) Gonadotropin-releasing hormone agonist versus human chorionic gonadotropin as a trigger of ovulation in polycystic ovarian disease gonadotropin hyperstimulated cycles. *Fertil. Steril.*, **62**, 35–41.

Larsson-Cohn, U, Fahraeus, L, Wallentin, L. *et al.* (1981) Lipoprotein changes may be minimized by proper composition of a combined oral contraceptive. *Fertil. Steril.*, **35**, 172–179.

Leeton, J., Trounson, A. and Jessup, D. (1985) Support of the luteal phase in *in vitro* fertilization programs: results of a controlled trial with intramuscular Proluton. *J. In Vitro Fertil. Embryo Transfer*, **2**, 166–169.

Lenton, E.A., Sulaiman, R., Sobowale, O. *et al.* (1982) The human menstrual cycle: plasma

Downloaded from https://academic.oup.com/humrep/article/15/suppl_1/129/716192 by Dokuz Eylul University Library (DEU) user on 02 September 2021

concentrations of prolactin, LH, FSH, oestradiol and progesterone in conceiving and non-conceiving women. *J. Reprod. Fertil.*, **65**, 131–139.

Martinez-Frias, M.L., Rodriguez-Pinilla, E., Bermejo, E. *et al.* (1998) Prenatal exposure to sex hormones: a case-control study. *Teratology*, **57**, 8–12.

Maxson, W.S. and Hargrove, J.T. (1985) Bioavailability of oral micronized progesterone. *Fertil. Steril.*, **44**, 622–626.

Miles, R.A., Paulson, R.J., Lobo, R.A. *et al.* (1994) Pharmacokinetics and endometrial tissue levels of progesterone after administration by intramuscular and vaginal routes: a comparative study. *Fertil. Steril.*, **62**, 485–490.

Mores, N., Krsmanovic, L.Z. and Catt, K.J. (1996) Activation of LH receptors expressed in GnRH neurons stimulates cyclic AMP production and inhibits pulsatile neuropeptide release. *Endocrinology*, **137**, 5731–5734.

Nader, S., Berkowitz, A.S., Ochs, D. *et al.* (1988) Luteal-phase support in stimulated cycles in an *in vitro* fertilization/embryo transfer program: progesterone versus human chorionic gonadotropin. *J. In Vitro Fertil. Embryo Transfer*, **5**, 81–84.

Nahoul, K., Dehennin, L. and Scholler, R (1987) Radioimmunoassay of plasma progesterone after oral administration of micronized progesterone. *J. Steroid Biochem.*, **26**, 241–249.

Nahoul, K., Dehennin, L., Jondet, M. *et al.* (1993) Profiles of plasma oestrogens, progesterone and their metabolites after oral or vaginal administration of estradiol or progesterone. *Maturitas*, **16**, 185–202.

Nikkanen, V., Kresanov, I., Makinen, J. *et al.* (1992) The effect of luteal support with human chorionic gonadotrophin or progesterone on the daily progesterone profile after different types of ovarian stimulation. *Hum. Reprod.*, **7**, 333–336.

Nora, J.J. and Nora, A.H. (1973) Birth defects and oral contraception. *Lancet*, **i**, 941–942.

Nora, J.J., Nora, A.H., Blu, J. *et al.* (1978) Exogenous progestogen and oestrogen implicated in birth defects. *J. Am. Med. Assoc.*, **240**, 837–843.

Norman, T.R., Morse, C.A. and Dennerstein, L. (1991) Comparative bioavailability of orally and vaginally administered progesterone. *Fertil. Steril.*, **56**, 1034–1039.

Olivennes, F., Fanchin, R., Bouchard, P. *et al.* (1995) Scheduled administration of a gonadotrophin-releasing hormone antagonist (Cetrorelix) on day 8 of in-vitro fertilization cycles: a pilot study. *Hum. Reprod.*, **10**, 1382–1386.

Penarrubia, J., Balasch, J., Fabregues, F. *et al.* (1998) Human chorionic gonadotrophin luteal support overcomes luteal phase inadequacy after gonadotrophin-releasing hormone agonist-induced ovulation in gonadotrophin-stimulated cycles. *Hum. Reprod.*, **13**, 3315–8.

Polson, D.W., Rogers, P.A., Krapez, J.A. *et al.* (1992) Vaginal progesterone as luteal phase support in an IVF/GIFT programme. *Eur. J. Obstet. Gynecol. Reprod. Biol.*, **46**, 35–38.

Pouly, J.L., Bassil, S., Frydman, R. *et al.* (1997) Support de la phase lutéale par la progestérone vaginale: étude comparative avec la progestérone micronisée per os. *Contracept-Fertil-Sex.*, **25**, 596–601.

Resseguie, L.J., Hick, J.F., Bruen, J.A. *et al.* (1985) Congenital malformations among offspring exposed *in utero* to progestins, Olmsted County, Minesota, 1936–1974. *Fertil. Steril.*, **43**, 514–519.

Ross, D., Cooper, A.J., Pryse-Davies, J. *et al.* (1997) Randomized, double-blind, dose-ranging study of the endometrial effects of a vaginal progesterone gel in oestrogen-treated postmenopausal women. *Am. J. Obstet. Gynecol.*, **177**, 937–941.

Rothman, K.J., Fyler, D.C., Goldblatt, A. *et al.* (1979) Exogenous hormones and other drug exposures of children with congenital heart disease. *Am. J. Epidemiol.*, **109**, 433–439.

Simón, J.A., Robinson, D.E., Andrews, M.C. *et al.* (1993) The absorption of oral micronized progesterone: the effect of food, dose proportionality, and comparison with intramuscular progesterone. *Fertil. Steril.*, **60**, 26–33.

Smith, E.M., Anthony, F.W., Gadd, S.C. *et al.* (1989) Trial of support treatment with human chorionic gonadotrophin in the luteal phase after treatment with buserelin and human menopausal gonadotrophin in women taking part in an *in vitro* fertilisation programme. *Br. Med. J.*, **298**, 1483–1486.

Smitz, J., Devroey, P., Camus, M. *et al.* (1988) The luteal phase and early pregnancy after combined GnRH-agonist/HMG treatment for superovulation in IVF or GIFT. *Hum. Reprod.*, **3**, 585–590.

Smitz, J., Devroey, P., Faguer, B. *et al.* (1992a) A prospective randomized comparison of

Downloaded from https://academic.oup.com/humrep/article/15/suppl_1/129/716192 by Dokuz Eylul University Library (DEU) user on 02 September 2021

intramuscular or intravaginal natural progesterone as a luteal phase and early pregnancy supplement. *Hum. Reprod.*, **7**, 168–175.

Smitz, J., Erard, P., Camus, M. *et al.* (1992b) Pituitary gonadotrophin secretory capacity during the luteal phase in superovulation using GnRH-agonists and HMG in a desensitization or flare-up protocol. *Hum. Reprod.*, **7**, 1225–1229.

Smitz, J., Bourgain, C., Van Waesberghe, L. *et al.* (1993) A prospective randomized study on oestradiol valerate supplementation in addition to intravaginal micronized progesterone in buserelin and HMG induced superovulation. *Hum. Reprod.*, **8**, 40–45.

Soliman, S., Daya, S., Collins, J. *et al.* (1994) The role of luteal phase support in infertility treatment: a meta-analysis of randomized trials. *Fertil. Steril.*, **61**, 1068–1076.

Srivastava, R.K., Luu-The, V., Marrone, B.L. *et al.* (1994) Suppression of luteal steroidogenesis by an LHRH antagonist (Nal-Lys antagonist: antide) *in vitro* during early pregnancy in the rat. *J. Mol. Endocrinol.*, **13**, 87–94.

Steege, J.F., Rupp, S.L, Stout, A.L. *et al.* (1986) Bioavailability of nasally administered progesterone. *Fertil. Steril.*, **46**, 727–729.

Stovall, D.W., Van Voorhis, B.J., Mattingly, K.L. *et al.* (1996) The effectiveness of sublingual progesterone administration during cryopreserved embryo transfer cycles: results of a matched follow-up study. *Fertil. Steril.*, **65**, 986–991.

Trounson, A., Howlett, D., Rogers, P. *et al.* (1986) The effect of progesterone supplementation around the time of oocyte recovery in patients superovulated for *in vitro* fertilization. *Fertil. Steril.*, **45**, 532–535.

Van Steirteghem, A.C., Smitz, J., Camus, M. *et al.* (1988) The luteal phase after in-vitro fertilization and related procedures. *Hum. Reprod.*, **3**, 161–164.

Yovich, J.L., McColm, S.C., Yovich, J.M. *et al.* (1985) Early luteal serum progesterone concentrations are higher in pregnancy cycles. *Fertil. Steril.*, **44**, 185–189.

Downloaded from https://academic.oup.com/humrep/article/15/suppl_1/129/716192 by Dokuz Eylul University Library (DEU) user on 02 September 2021