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Steroids 65 (2000) 671–679

Steroids

Progesterone and progestins: applications in gynecology

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Abstract

Achievements obtained in infertility treatments over the past two decades have sparked interest in optimizing progesterone administration. Although progesterone is absorbed orally when ingested in micronized form, bioavailability is poor because of extensive liver metabolism. This explains why full predecidual transformation of the endometrium cannot be achieved with oral progesterone and is therefore ineffective for luteal support in in vitro fertilization (IVF). Progesterone administered non-orally can duplicate the endometrial changes normally seen in the menstrual cycle in women whose ovaries are inactive. Similar results have been reported with intramuscular (i.m.) injections and vaginal administration, although tissue levels are higher in the latter case. The recent development of a controlled and sustained release vaginal progesterone gel, Crinone® 8%, has made the vaginal route clinically practical by limiting the number of necessary applications to 1 per day. This regimen has been found at least as effective as intramuscular (i.m.) injections in women whose ovaries are inactive (donor egg IVF) and for luteal support in regular IVF. Hence, painful daily i.m. injections of progesterone in oil become unnecessary. The possibility of reducing the number of daily applications of vaginal progesterone to 1 per day, made possible by the sustained release gel Crinone, has opened new possibilities for long-term treatments, as in hormone replacement therapy (HRT). The low incidence of systemic side effects with use of the vaginal progesterone gel used for HRT in amenorrheic women, contrasts with findings related to use of synthetic progestins. Preliminary data suggest that vaginal progesterone can be instrumental in enhancing the notoriously poor long-term compliance of HRT. © 2000 Published by Elsevier Science Inc.

Keywords: Progesterone; Luteal support; Endometrial receptivity; HRT

1. Introduction

Progesterone and notably vaginal progesterone has been used for many years for indications such as luteal phase defect and premenstrual syndrome (PMS) [1]. The advent of modern infertility treatments has expanded the use of physiological progesterone replacement. In infertility, the best study paradigm has been the egg donation model. There, in the absence of an endogenous source of progesterone, the challenge was to prime endometrial receptivity with the sole help of exogenous hormones.

Today, considerable data have accumulated, providing a wealth of information and offering compelling evidence for the efficacy of exogenous progesterone administered non-orally, either vaginally or by i.m. injections [2]. Both forms of treatment succeeded in duplicating the complete sequence of endometrial changes normally seen in the luteal phase of the menstrual cycle, although some have claimed [3] that vaginal progesterone may be more reliable.

From donor egg data, we learned that the duration of exposure, rather than actual levels of progesterone, controls the normal sequencing of secretory transformations in the endometrium and the proper priming of receptivity to embryo implantation. Furthermore, contrary to early expectations, the estradiol to progesterone (E_2/P) ratio has appeared to have little bearing on endometrial morphology. However, the view disclaiming a role of E_2/P ratio must be reconsidered when uterine contractility is taken into account.

Finally, a direct vagina-to-uterus transport phenomenon or '*first uterine pass effect*' has been found in the study of vaginal administration of progesterone. This vaginal route paradox became most prominent when daily dosing of vaginal progesterone was reduced with the use of a new controlled and sustained vaginal progesterone gel, Crinone®;

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PII: S0039-128X(00)00123-9

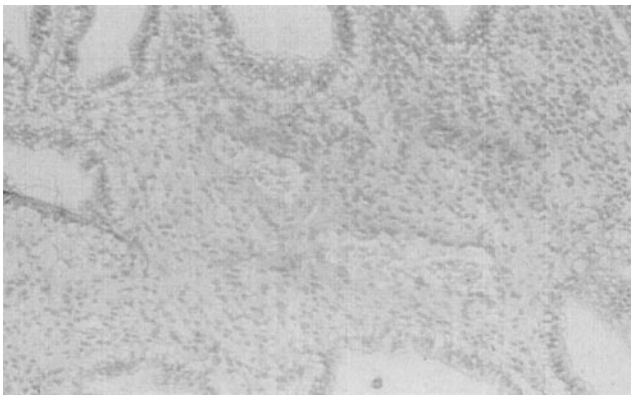

Fig. 1. Secretory transformation of endometrial glands. Under the influence of progesterone, endometrial glands undergo serial changes that characterize the first days of the luteal phase. Characteristically, sub-nuclear glycogen filled vacuoles develop and push nuclei upward. This gives a typical 'palisade' appearance to the glandular epithelium.

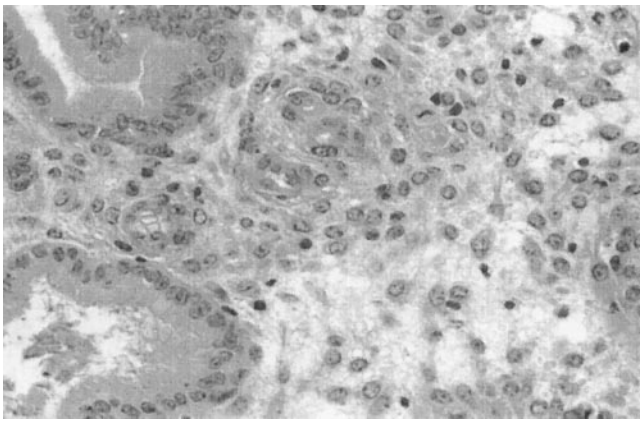

Fig. 2. Secretory transformation of endometrial stroma. The later stages of the luteal phase are characterized by changes occurring in the stroma. Characteristically, stromal cells undergo predecidualization, which becomes complete by cycle days 24 to 26.

the result was lower plasma levels [4] but similar endometrial effects.

2. Control of secretory changes by endogenous or exogenous progesterone: the donor egg model

Originally a mere spin off of in vitro fertilization (IVF), donor egg IVF in women whose ovaries are inactive has turned out to be a formidable test bench for studying the impact of hormones on the control of endometrial receptivity [5–8].

In early work, Rosenwaks [7] showed that the optimal time for 2-to-8-cell embryo transfer (ET) was on days 17 and 18 of treatment cycles, in which progesterone was started on cycle day 15. Conversely, it was later shown that transfer of frozen blastocycsts showed good results when transfers occurred on the 5th day of progesterone treatment [9]. Experimental studies in the donor egg model determined that great flexibility existed in follicular phase length. The estrogen only phase of the treatment could harmlessly vary from as little as 7 days to as much as one month [10–12] or possibly longer.

Schematically, the secretory transformation of the endometrium under the influence of progesterone can be divided in two phases. The early phase (days 15–20) is characterized by transformations occurring in endometrial glands. These glandular changes have served as a landmark for 'dating' the endometrium during the first part of the luteal phase. At this early step of the luteal phase, the most emblematic changes are the coiling of glands and the sub-nuclear development of glycogen-filled vacuoles. These push glandular nuclei upward, thereby conferring a 'palisade'-like appearance to the lining of the glandular epithelium (Fig. 1).

In the menstrual cycle, sub-nuclear vacuoles represent a transitory finding characteristic of cycle days 17 to 18. On day 20, i.e. on the 6th day of exposure to post-ovulatory progesterone, glycogen vacuoles have moved upward toward the apex of the glandular cells letting nuclei regain their original basal position. In E_2 and progesterone cycles, investigators have universally observed a prolonged persistence of sub-nuclear vacuoles that commonly remain fully visible on cycle day 20. In E_2 and progesterone cycles, all functional parameters of endometrial glands follow the delay seen in the morphologic transformation of endometrial glands. Notably, estrogen receptor (ER) and progesterone receptors (PR) remain fully visible in the nuclei of the glandular epithelium on the 6th day of exposure to progesterone, whereas, usually, they have disappeared on Day 20 of the menstrual cycle. Later in the luteal phase, morphologic changes induced by progesterone predominate in the stroma. These culminate in the predecidual transformation of stromal cells on cycle days 24 to 26 (Fig. 2).

The early luteal phase is also associated with characteristic changes of endometrial appearance visible on ultrasound. Under the influence of E_2 (endogenous or exogenous), the endometrium takes a characteristic hypoechogenic appearance, which is less echogenic than the surrounding myometrium. This appearance confers the classic '3 lines' profile generated by both (near and far) myometrial-endometrial interphases and the virtual uterine cavity.

Under the influence of endogenous [13] or exogenous progesterone [14], the endometrium acquires a characteristic hyperechogenic appearance. These changes originate in the basal area of the surface over time. Computerized measurements of endometrial changes in echogenicity have been attempted. Leibovitz et al. calculated a relative echogenicity coefficient, which displayed linear increase after ovulation [15]. Hence, these data confirmed prior work of Grunfeld et al. conducted in the donor egg model [13]. More recently, Fanchin et al. [16] used a somewhat similar approach and measured the progressive increase in endometrial echogenicity that expands from the basis of the endometrium toward the surface (Fig. 3). They expressed their

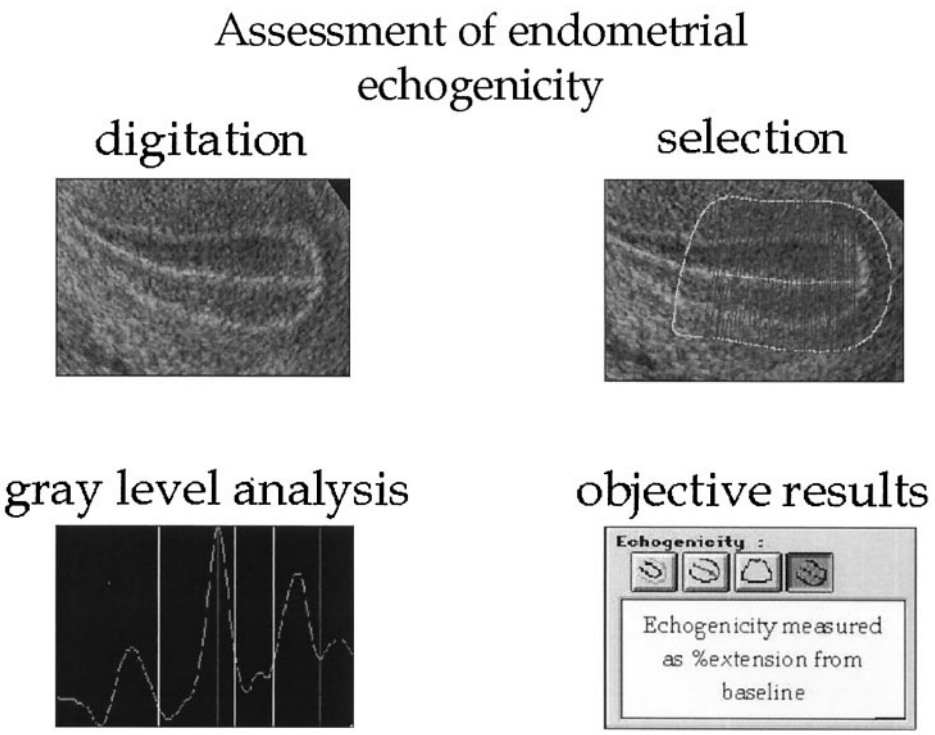

Fig. 3. Assessment of endometrial echogenicity. Under the influence of progesterone the hyperechogenic transformation starts at the base of the endometrium and expands upward toward the endometrial surface. A computer-assisted method was used to quantify the degree of upward extension of endometrial echogenicity. Results are expressed as percentage of extension of hyperechogenicity [16].

results in the percentage of hyperechogenicity in relation to total endometrial surface. In this model, the 'hypoechogenic' looking endometrium characteristic of the follicular phase scored 30%, whereas fully 'hyperechogenic' patterns seen in the luteal phase scored from 70 to 100%.

The parallel analysis of timed sequences of hyperechonegic changes and histologic findings made in the endometrium suggest hyperechogenicity results from coiling of endometrial glands. According to this hypothesis, straight glands of the follicular phase run parallel to ultrasound beams, whereas coiling of mucus-filled glands increases the number of sound interfaces and, consequently, echogenicity. Conversely, stromal changes occurring in the late luteal phase don't seem to have specific echographic expressions. Immediately before menses (1–2 days), the endometrium loses its homogenous hyperechogenic appearance to take a characteristic patchy appearance, where hyper- and hypoechogenic areas alternate.

3. The need for luteal support in infertility treatments

There now is a wealth of data supporting the need for luteal support in controlled ovarian hyperstimulation (COH) cycles, such as used in IVF-embryo transfer (IVF-ET) [17]. The reasons for prescribing luteal support revolve around documented fears that progesterone production becomes unregulated when ovulation is triggered with hCG [18]. Other reasons for luteal support include the down regulation of gonadotropins with analogues of GnRH (GnRH-a), and aspiration of follicular fluid and/or granulosa/luteal cell masses [19,20]. The first approach for luteal support involved enhancing and/or supporting the endogenous production of progesterone with repeated administrations of hCG. Despite proven efficacy, this approach significantly increases the risk of frank ovarian hyperstimulation syndrome (OHSS) [21,22]. Recently, hCG for luteal support has been abandoned due to the risks of OHSS and the availability of alternative treatments. Exogenous progesterone has been used for many years as an alternative option for luteal support in infertility treatments. Repeated intramuscular (i.m.) injections of progesterone in peanut or sesame oil solutions have been found effective for correcting luteal phase defect in the natural cycle [23], as well as for luteal support in COH [19,24]. Progesterone injections that need to be repeated daily or twice daily are, however, notoriously painful and may result in frequent serious adverse conditions such as sterile abscesses. Hence, alternate routes of administration have been sought for practical reasons, to avoid the cumbersome character of i.m. progesterone.

3.1. Oral progesterone

Progesterone is nearly entirely absorbed after oral ingestion when prepared in micronized form. Yet, be-

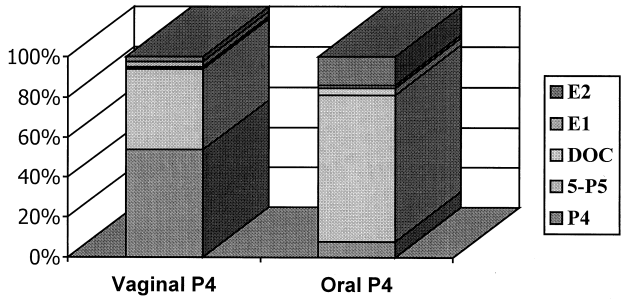

Fig. 4. Oral and vaginal progesterone. Serum levels of progesterone and progesterone metabolites after vaginal and oral administration of 100 mg of progesterone. Oral progesterone only results in minimal elevation of plasma progesterone with the majority of the ingested dose transformed in 5α-reduced products. The measured products are estradiol (E_2), estrone (E_1), desoxycorticosterone (DOC), 5α-dehydroprogesterone (5-P_5), and progesterone (P_4).

cause of intense inactivation by metabolism during first liver pass, the bioavailability of oral progesterone is notoriously poor at $<$10% [25]. This poor bioavailability explains that despite the large amounts used (up to 600 mg/day), oral progesterone fails to trigger the full array of endometrial changes seen in the late luteal phase of the menstrual cycle. Particularly, the last step of these changes (the predecidual transformation of stroma cells) fails to be induced by oral progesterone [3].

Some confusion has existed over these findings. Early reports claimed high plasma progesterone levels after oral administration of progesterone. However, fairly low plasma levels of progesterone have been reported when the hormone is given orally, and proper assays are used. Circulating levels of progesterone and its metabolites, determined by sufficiently specific assays, after oral and vaginal administration of 100 mg of progesterone are illustrated in Fig. 4. As can be seen, when taken orally, progesterone accounts for less than 10%, whereas most of ingested progesterone is transformed to 5α-reduced metabolites. The metabolites of progesterone that bind to the $GABA_A$ receptor complex are responsible for drowsiness and other neurologic side effects. Interestingly, however, erroneous readings of circulating progesterone have been obtained after oral intake of progesterone when plasma levels are measured by direct radio-immunoassays. Direct assays have only been validated for measurements of progesterone in the luteal phase of the menstrual cycle. After oral ingestion, the unusually high levels of progesterone metabolites alter the validity of progesterone measurements by direct assays because antibody specificity is insufficient in these unusual circumstances. Conversely, when progesterone is measured after separation on celite columns, plasma progesterone levels are low after oral ingestion; these low levels are concordant with the incomplete secretory transformation of the endometrium observed [25,26].

3.2. Non-oral progesterone

Because of the first liver pass effect with oral progesterone, luteal support in infertility treatments first utilized i.m. injections. Notably, i.m. progesterone is given to donor egg recipients whose ovaries are inactive [27,28]. Yet, the inconvenience of daily i.m. injections has fueled interest in alternate non-oral forms of administration. Progesterone given transdermally fails to achieve detectable levels and effects [29] due to poor skin permeability of progesterone and the large quantity needed to duplicate mid-luteal production by the corpus luteum (25 mg/24 h). Hence, although systems have been developed to deliver synthetic progestins transdermally, delivery of physiologic amounts of 'natural' progesterone through the skin is not a forseeable option. Similarly, repeated daily administration of nasal progesterone failed to induce predecidual changes of endometrial stroma, a finding in accordance with the low levels of plasma progesterone achieved (from 2 to 5 ng/ml).

3.3. Vaginal progesterone in infertility treatments

Because transdermal administration of progesterone is impractical, the vaginal route has long been regarded as the best, if not the only, alternate option for delivering progesterone non-orally to women. With the advent of IVF and other assisted reproductive procedures, interest has refocused on vaginal progesterone. Ultimately, the data suggest that vaginal progesterone is more than merely a non-oral alternative. Early work undoubtedly showed the high efficacy of vaginal progesterone at duplicating all the endometrial changes of the luteal phase. We now know, however, that this is not solely dependent on plasma levels, which remain lower than seen in the luteal phase of the menstrual cycle [30,31].

Initially, the vaginal progesterone used in infertility treatment required multiple daily administrations of locally made preparations (suppositories) that lacked pharmaceutical grade quality controls. An alternate option was progesterone-filled soft gelatin capsules, originally designed for oral use. The development of a controlled, sustained-release vaginal gel, Crinone, applied once a day, has made the vaginal route a viable option in many clinical situations; Crinone also provides luteal support in infertility treatment. Reducing the number of doses and the total amount administered underscored the unexpected uterine trophicity of this route of administration [4]. In a dose ranging study, Fanchin et al. [4] observed that administration of the Crinone gel, 4%, containing 45 mg of progesterone, every 2 days, resulted in plasma progesterone levels ranging from approximately 1 ng/ml to just under 5 ng/ml (Fig. 5). Despite these low levels of progesterone, which are in the 'luteal phase defect' range, early (day 20) and late luteal phase (day 24) endometrial biopsies were in phase and concordant with luteal phase findings of the menstrual cycle [4].

The discrepancy between low plasma progesterone lev-

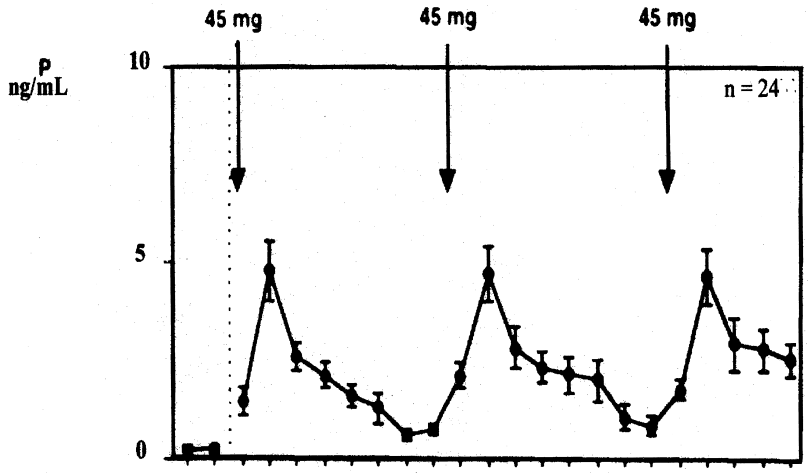

Fig. 5. Plasma progesterone levels after Crinone® 4% (45 mg). Every-2-day administration of the controlled and sustained release vaginal progesterone gel, Crinone results in subphysiological levels of plasma progesterone.

els and high uterine efficacy led us to postulate some degree of direct vagina-to-uterus transport or 'first uterine pass effect.' Supporting this hypothesis, Miles et al. reported higher uterine tissue concentrations of progesterone after vaginal administration than after i.m. injections, despite the lower plasma levels achieved in the latter case [32]. More recently, Cicinelli and his coworkers confirmed these findings in endometrial tissue obtained from hysterectomy specimens. Hence, their data excluded the possibility that endometrial findings represented contamination by progesterone present in the vagina [33].

Although the mechanism underlying the direct vagina-to-uterus transport of vaginal progesterone remains a source of debate, definitive progress has recently been made in clarifying the possibilities. Bulletti et al. used an original human ex-vivo model to study the direct vagina-to-uterus transport [34]. These authors showed that 3H progesterone applied on vaginal tissue, that remained attached to the uterus after hysterectomy, was transported directly to the fundal area of the uterus. Radioactivity peaked in the venous effluent approximately 1 to 2 h after the placement of 3H progesterone on the rim of vaginal tissue. In contrast, peak concentration in uterine tissue was observed after approximately 5 to 6 h. Because the perfusion system is an open one (no recirculation), these findings confirmed that 3H progesterone traveled directly from the vagina to the uterus. Trying to explain these counter intuitive findings, Cicinelli et al. [35] alluded to a possible mechanism for the direct vagina-to-uterus transport phenomenon observed. These authors studied the effects of vaginal administration of progesterone before performing a hysterectomy. They observed that the progesterone concentration in the uterine artery largely exceeded concentrations in the peripheral circulation. This observation suggests a possible vaginal/uterine veins-to-uterine artery diffusion; this ultimately causes a countercurrent exchange resulting in an elective transport of progesterone to the uterine fundus. Further work is needed to confirm this hypothesis.

Extensive experience has now been gained with the vaginal progesterone gel Crinone for luteal support in IVF. In donor egg recipients receiving Crinone, twice [36] and once [37] a day, endometrial changes and pregnancy rates were similar to those receiving 50 mg progesterone daily i.m. In regular IVF, data have been accumulated on 1251 cycles. Overall clinical pregnancy rates/transfer were 35.2%, a value slightly higher than found in historical controls under 35 years of age (31.5%).

Two groups compared their data to concomitant controls receiving luteal support from i.m. progesterone. Chantilis et al. [38] observed clinical and ongoing pregnancy rates of 40.4% and 36.2%/transfer in women receiving Crinone, and 44.4% and 36.1% in those having i.m. injections, respectively (women $<$ 35). Similarly, Schoolcraft et al. [39] observed clinical pregnancy rates/transfer of 60.4% in women who received luteal support from daily administrations of Crinone 8%. Clinical pregnancy rates were 60.9%/transfer in women receiving daily i.m. injections of 50 mg progesterone for luteal support. In historical controls receiving the same i.m. dose, the pregnancy rates/transfer were 63.4% and 63.9%/transfer for women $<$35 years old and 35 to 39 years old, respectively. Live birth rates were 55.8% and 56.5% in women receiving luteal support from Crinone or i.m. injections of progesterone, respectively.

Based on data described above, daily administration of the vaginal gel Crinone 8% can advantageously replace painful i.m. injections of progesterone for luteal support in donor egg and regular IVF.

3.4. Uterine contractility and uterine receptivity

Prior work has shown that the E_2 to progesterone ratio does not affect endometrial morphology, which is solely dependant on proper E_2 priming followed by the sequence

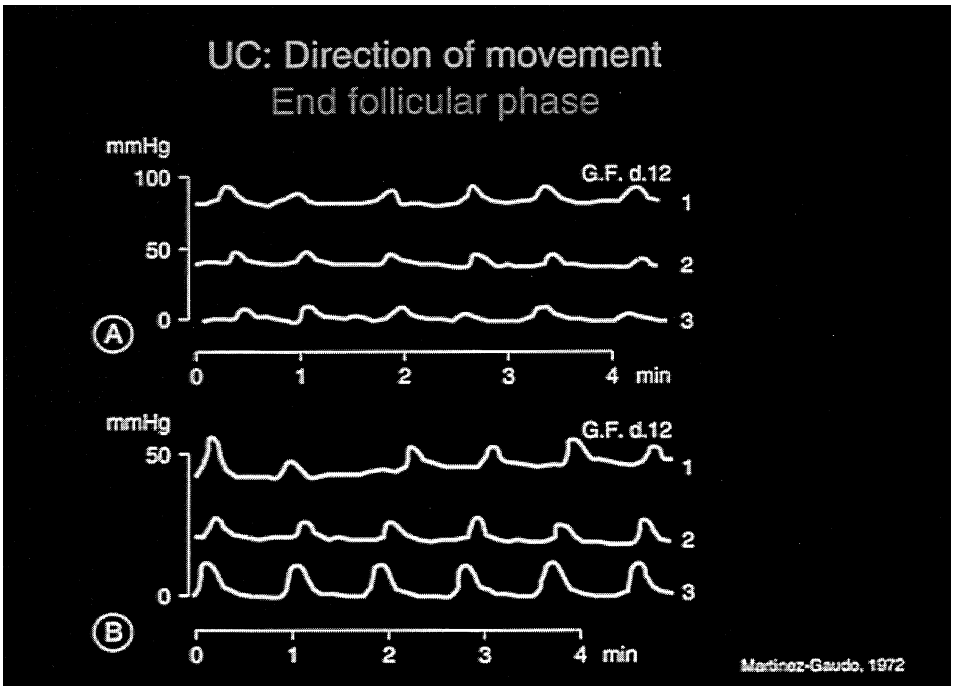

Fig. 6. Uterine contractions: late follicular phase. The late follicular phase is characterized by a high frequency of uterine contractions.

of effects triggered by progesterone [40–43]. Nevertheless, the E_2 to progesterone ratio does have an effect on uterine receptivity. Recent data, made available by direct visualization of uterine contractions on ultrasound, have revived the role of uterine contractility on uterine receptivity. In the menstrual cycle, the follicular phase is characterized by frequent peristaltic contractions that are mainly oriented from the cervical to the fundal end (retrograde contraction) [44]. Fig. 6 illustrates the typical pattern of contractility observed in the late follicular phase, as evidenced by a direct recording of intra-uterine pressure. This form of contractility, believed to depend on estrogen levels, probably participates in the transport of sperm toward the distal end of the fallopian tubes where fertilization occurs. Contrasting with the highly contractile pattern seen in the late follicular phase, the luteal phase is characterized by uterine quiescence [44] (Fig. 7). In IVF cycles, however, Fanchin et al. [45] observed a far higher level of contractility at the time of ET than normally seen in the luteal phase. In this study, a sizeable fraction of women had more than six uterine contractions/minute at the time of ET. Although the general characteristics of these women and their response to COH were not different from those whose uteri were quiescent, their IVF outcome was markedly poorer. As illustrated in Fig. 8, women who had two or less uterine contractions/min had a pregnancy rate in excess of 60% per transfer. It is possible that the excess contractility witnessed in these IVF patients results from the excessive levels of E_2 and altered E_2 to progesterone ratios. It remains to be established whether substances that exert utero-relaxing effects may improve pregnancy rates in IVF. We are currently investigating the question of whether early progesterone replacement in IVF can lower uterine contractility at the time of ET and improve IVF outcome. Preliminary data [46] showed that initiation of luteal support with Crinone 8% on the day of oocyte retrieval resulted in a lower level of uterine contractions at the time of transfer, which was associated with a strong trend toward higher pregnancy rates. These data support early onset of Crinone treatment, such as on the day of oocyte retrieval, for maximizing uterine quiescence at the time of ET and optimizing pregnancy rates.

3.5. Vaginal progesterone in gynecology: a side effect-free option for HRT

The development of the controlled and sustained release vaginal progesterone gel Crinone, which limits daily dosing to one application per day, has created new possibilities for long-term use of vaginal progesterone, notably in HRT. Synthetic progestins have been conceived to resist enzymatic degradation in the liver and remain active when administered orally. Yet synthetic progestins, and particularly the two most widely used products, medroxyprogesterone acetate (MPA) and norethisterone acetate (NETA), have only been tested for their ability to duplicate the genomic effects of progesterone; specifically, they are able to antagonize the proliferative effects of estrogens on the endometrial epithelium and prevent endometrial hyperplasia and cancer [47–49]. There is ample evidence that both MPA and NETA are highly effective in this respect.

Progesterone has recently been shown to exert non-genomic effects by directly binding the cell membrane and/or after local or distant metabolism to 5α-reduced products [50]. The lead product among 5α-reduced metabolites,

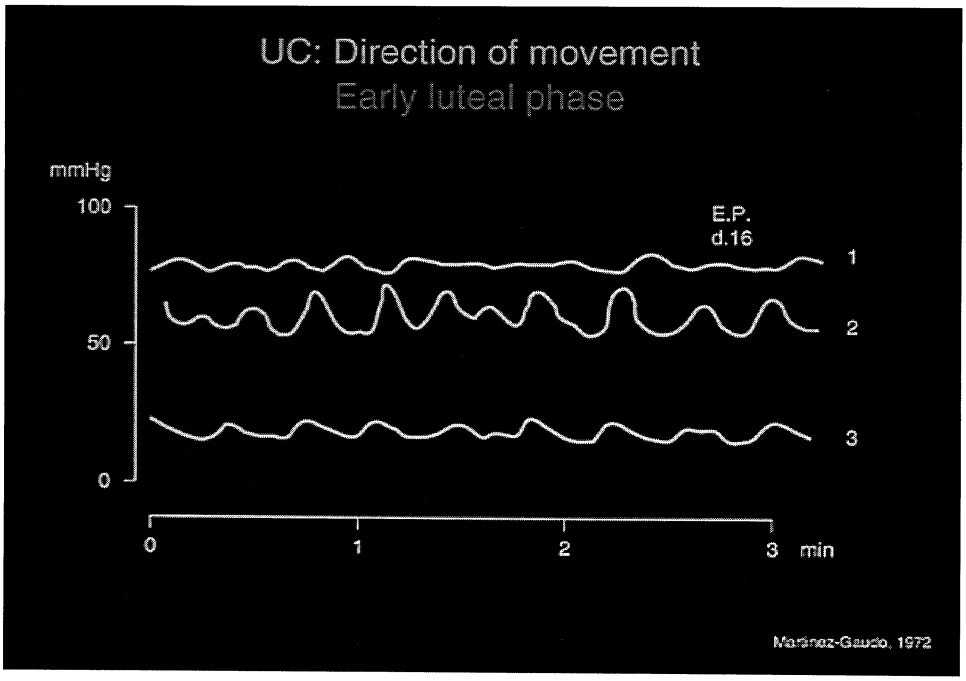

Fig. 7. Uterine contractions: luteal phase. The luteal phase is characterized by uterine quiescence.

allopregnanolone, binds to the hormonal site of the membrane bound $GABA_A$ receptor complex and activates influx of Cl^- ions into the cell. This raises the resting potential and, ultimately, decreases cellular excitability. In the CNS, where these properties of progesterone were first unveiled, the net result of non-genomic effects of progesterone are tranquilizing and sedation effects [51–53]. When individuals are exposed to higher than normal levels of progesterone metabolites, such as after oral ingestion of progesterone, true somnolence can occur [54,55]. This may ultimately lead to unpleasant sleep disturbances (feeling drowsy all the time and never rested).

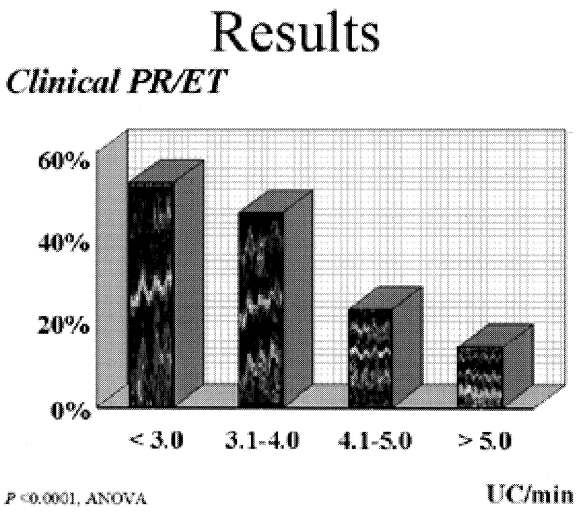

Fig. 8. Uterine contractions and uterine receptivity. A fraction of IVF patients present increased uterine contraction (UC) frequency at the time of embryo transfer (ET). This seriously hampers IVF outcome, or pregnancy rates (PR). Early onset of progesterone supplementation (day of oocyte retrieval) decreases uterine contraction frequency at the time of ET (results not shown).

Non-genomic properties of synthetic progestins were not tested when these products were designed; therefore, their actual non-genomic effects are anyone's guess. The best studied of the synthetic progestins, MPA, does not activate the $GABA_A$ receptor complex. Although MPA can undergo 5α-reduction and 3α-hydroxylation just like progesterone (under the influence of the same enzymes), the resulting product modified (like allopregnanolone), fails to bind the GABA receptor [56]. This may be due to changes in the spatial conformation of the molecule, which occur when the acetate radical is added at the other end of the molecule, in 17-position.

Because progesterone is endogenously produced in the CNS of both men and women, MPA and its metabolites may disturb the natural properties of endogenously produced progesterone (natural tranquilizers). Hence, synthetic progestins, such as MPA, by disrupting the action of endogenously produced psychotropic metabolites of progesterone, may generate negative side effects, especially, in mood sensitive individuals. The mechanisms described above are likely to be the main explanation for the notoriously cumbersome psychological side effects of synthetic progestins, notably MPA [57].

Contrary to findings made with synthetic progestins, the vaginal progesterone gel is characteristically devoid of psychological side effects [58,59]. Therefore, we studied vaginal gel in HRT. Two regimens were used [60]. First, the

vaginal gel Crinone, 4%, was administered daily in a cyclical HRT regimen. This regimen resulted in predictable withdrawal bleeding in over 90% of treated women. In the second regimen, the progesterone gel was administered twice weekly on the days transdermal E_2 skin patches were changed (when Crinone was used in conjunction with transdermal E_2). This regimen took advantage of Crinone's sustained release properties and reduced the number of vaginal applications. Here, the majority of women were and remained amenorrheic throughout the first 6 months of their treatment. In 18 women who stayed on this regimen for up to 18 months, 16 remained completely amenorrheic. Because of the lack of side effects of vaginal progesterone [59] and its satisfactory control of uterine bleeding, long-term vaginal progesterone should enhance compliance in women on HRT. The vaginal progesterone option is particularly indicated for women prone to experience subjective side effects with synthetic progestins.

4. Conclusion

Vaginal administration of progesterone, originally seen as the only practical alternative to daily i.m. injections, ultimately unveiled unexpected direct transport of progesterone to the uterus or 'uterine first pass effect.' This explains the highly predictable endometrial effects seen with vaginal progesterone.

The development of the controlled and sustained release vaginal progesterone gel Crinone, which limits dosing to once a day, has made the vaginal route clinically acceptable for a variety of options. In infertility treatment, Crinone 8% effectively provides luteal support in donor egg and regular IVF programs. In HRT, cyclical (10 days/month) and constant combined (two times/week) administration of Crinone 4% provided satisfactory control of bleeding whereas avoiding the side effects seen with synthetic progestins.

Acknowledgments

Expert secretarial assistance was provided by Stephanie Roy. Illustrations were prepared by Nihal Benaïssa. The help of both is greatly acknowledged.

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