

# The Use of Progesterone and Fertility Treatment

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### I. INTRODUCTION

I first became interested in progesterone during my fellowship at The University of Texas Southwestern Medical School where I worked with Dr. Paul MacDonald. During my fellowship, I learned that progesterone was in fact a 21-carbon molecule, which had a double bond between the 4 and 5 carbons, as well as ketone groups at the 3-carbon and the 20-carbon. It was during this time that I worked on the metabolism of progesterone, and specifically, the 5 $\alpha$ -reduced metabolite known as 5 $\alpha$ -dihydroprogesterone. Ultimately, we found that the 3 $\alpha$ - and 3 $\beta$ , 6 $\alpha$ -dihydroxy, 5 $\alpha$ -reduced pregnane-20-one molecules were the principle metabolites of 5 $\alpha$ -dihydroprogesterone found in urine.

### II. PROGESTERONE

#### A. Production

Progesterone is a principle secretory product of corpus luteum. Its only known physiologic role is to prepare and maintain pregnancy. During the midluteal phase of the ovarian cycle, progesterone is secreted in amounts of 40-50 mg/day; and in the amounts of 250 mg/day or more during pregnancy. Outside of pregnancy, secretion is less than 1 mg/day. Among men or women during the follicular phase, prepubertal or post-menarcheal women, progesterone is secreted in tiny amounts compared to progesterone in the luteal phase or in pregnancy, when the progesterone is secreted in relatively enormous amounts compared to other hormones.

#### B. Metabolism

Progesterone metabolism is quite complicated. Until recently, only about 25% of progesterone could be accounted for, primarily through isolation of urinary metabolites. Today, we know that of serum progesterone (secreted by the corpus luteum), approximately half is metabolized by the liver and half is metabolized in the non hepatic or extra hepatic sites. Of that in the liver, approximately 25% is metabolized by 5 $\beta$ -reductase, and then acted on by other hormones to ultimately produce glucuronic acid-conjugated pregnanones, namely pregnanediol. The other half is metabolized by 5 $\alpha$ -reductase where it is ultimately conjugated with sulfate groups and excreted in the hepatobiliary circulation. In the gut, these progesterone metabolites are acted upon by microorganisms that contain enzymes foreign to the human and are metabolized to compounds that are unrecognizable by standard assays.

The other half of progesterone is metabolized in extrahepatic sites. Of these, 40% is reduced by 5 $\alpha$ -reductase. 5 $\alpha$ -reductase is found in a variety of sources, namely the skin. 9% of progesterone is metabolized by the 20 $\alpha$ -oxidoreductase, and 1% is metabolized by hydroxylase forming the deoxycorticosterone (DOC), which, of course, has mineralocorticoid properties. The 5 $\alpha$ -reduced and 20 $\alpha$ -reduced pathways are believed to produce progesterone metabolites, which produce a variety of bioresponses. Anesthetic properties have been found with certain progesterone metabolites such as the 5 $\alpha$ -reduced compounds. Alfaxalone, in fact, was a progesterone-metabolite anesthetic which was one of the earlier sedative agents used in Europe. 5 $\alpha$ -reduced compounds also have anxiolytic properties; pregnenolone is thought to have an anticonvulsant property. All of these compounds are believed to modulate neuronal activity through the gamma-aminobutyric acid (GABA) receptor that is found in widespread location throughout the brain. By modulating this receptor, neuronal activity can be increased or decreased, depending upon the conformation, which is induced after binding these metabolites.

## C. Luteal Phase Defect

### 1. Background.

Luteal phase dysfunction was first described by Dr. Georgiana Jones in 1949. We know from luteectomy studies that the luteal placental shift occurs between 7 and 9 weeks gestation. These early studies were conducted in pregnant women whereby the corpus luteum was removed at various stages between 7 and 9 weeks gestation. At 7 weeks gestation, spontaneous abortion occurred consistently, whereas at 9 weeks gestation, a pregnancy was usually spared. Based on these studies, the concept of the luteal placental shift occurring between 7 and 9 weeks gestation, was formed. Using the oocyte donation model, we know that progesterone and only progesterone is essential to preparation and maintenance of the pregnancy, after proper estrogen priming. Using this model, women with estrogen followed by estrogen and progesterone are able to produce term pregnancies. We have also learned through oocyte donation that, while progesterone levels typically start rising between 7 and 9 weeks gestation, there are a few stragglers who won't secrete progesterone in significant amounts from the placenta (as determined by serial progesterone levels), until 10 to 12 weeks gestation.

### 2. Diagnosis

Luteal phase deficiency is diagnosed through a variety of methods: basal body temperature charts, endometrial biopsies, progesterone levels, etc. Of course, the problem with any of these methods is the controversy surrounding the diagnosis of luteal phase defect, specifically determining whether or not a particular abnormal test which occurs in 1 cycle occurs in all cycles. In other words, is an abnormal test a sporadic occurrence that occurs in all women or is LPD truly a disease or syndrome that occurs in a majority of cycles?

Shown here is a standard slide evaluating progesterone levels during the luteal phase in fertile women. Typically, progesterone levels are obtained 7 days after the LH surge. While most fertile women have progesterone levels > 10 ng/mL, there are some presumably normal fertile women who have low progesterone. Another problem with progesterone levels, of course, is that secretion varies sometimes 5- to 10-fold over an hour, and is also episodic with respect to LH secretion from the pituitary gland.

### 3. Treatment

Luteal phase dysfunction is typically treated in one of four ways: progesterone supplementation, supraovulation (more follicles make more progesterone), hCG (which, of course, stimulates the corpus luteum to make more progesterone), or other causes such as hyperprolactinemia or thyroid disease. Progesterone is typically initiated during the luteal phase in a variety of methods, i.e., the third day after the basal body temperature rise, fourth day after LH surge, or after artificial insemination. Progesterone treatment through the 12th week of pregnancy is recommended to allow for a margin of safety.

## III. PROGESTERONE PRODUCTS

### A. Routes of Delivery

Progesterone treatment is found using a variety of delivery methods: vaginal progesterone, intramuscular progesterone, oral progesterone, and other less frequent vehicles such as transdermal, nasal and rectal progesterone.

Progesterone in oil is in widespread use. This product is made by Schein. Progesterone is dissolved in a sesame oil base and of course, the problem with this progesterone is that it is, in fact, injectable. Another potential problem is that this medication has a FDA mandated label which, if you read down below, states that there is an increased risk of minor birth defects in children whose mothers take this

drug during the first 4 months of pregnancy, specifically, genital abnormalities in male and female babies (hypospadias and clitoromegaly). Progesterone is also administered in a suppository form. Earlier suppositories were mixed with cocoa butter, which has a relatively low melting point and tends to be messy with nuisance complaints of vaginal discharge. Vaginal suppositories can also be mixed with a polyethylene glycol or PEG-base, which has a lower melting point. Nevertheless, vaginal discharge is also common with this type of base as well. Progesterone is also made in an oral form. Shown here is a wax matrix oral tablet, where the progesterone is mixed with a wax-like agent. Progesterone capsules are also found commonly consisting of micronized progesterone which is encapsulated or mixed with an inert compound and encapsulated, depending upon the dose. One form of oral progesterone found in Europe is called Utrogestan, where the progesterone is mixed with a gel-like oil. The problem with the oral progesterones is that absorption is variable depending upon particle size and hepatic metabolism. Because the quick absorption and rapid metabolism, administration needs to be given 3 times daily which leads to reduced compliance.

#### B. Side Effects

Progesterone has several side effects. Many physicians feel that progesterone in some women is responsible for premenstrual syndrome. Drowsiness is also well documented in oral progesterone administration. Progesterone allergy, or specifically sesame seed oil allergies have been well documented with the intramuscular route. Vaginal discharge is a problem encountered with vaginal suppositories. Dr. Luc Pouly and colleagues studied luteal support after in vitro fertilization comparing Crinone 8% to Utrogestan. They found an increased frequency of drowsiness in all patients using Utrogestan (the oral agent) when compared to vaginally administered Crinone. The control groups (Day 0) in all patients and pregnant patients were similar with respect to reports of drowsiness. On Days 4, 8, and 12, the oral progesterone had a nearly double frequency of reports of drowsiness. Progesterone allergy, or specifically sesame seed oil allergy, has been described. Another progesterone is also found commercially dissolved in a peanut oil, but this medication is about twice the cost.

### IV. CRINONE

#### A. The Case for Vaginal Progesterone

Why vaginal progesterone? Oral progesterone has poor bioavailability after hepatic metabolism. Incomplete secretory transformation of the endometrium occurs with oral progesterone, which is why oral progesterone is not used in oocyte donation. Oral progesterone also has been shown to induce sedative and hypnotic effects. Transdermal progesterone is not practical because of the poor skin permeability and inactivation in the skin due to 5 $\alpha$ -reductase. Intramuscular progesterone is, of course, very common during IVF luteal phase support and oocyte donation, but is uncomfortable and causes local pain and irritation and occasional sterile abscesses. Intramuscular progesterone has also been shown in one study to have lower uterine concentrations, when compared to vaginal progesterone. A study by Miles, Paulsen, and Lobo (1994) studied 20 women undergoing oocyte donation. They had a standard micronized estradiol step-up treatment followed by progesterone administered either vaginally in micronized capsules (200 mg every 6 hours), or intramuscular progesterone (50 mg/d). They found that intramuscular progesterone produced higher serum concentrations, but endometrial progesterone concentration was higher when the intravaginal progesterone was administered.

#### B. First Uterine Pass Model

This ultimately led to the development of a first uterine pass model which was studied by Columbia Research Laboratories (Dr. Buletti, Ziegler, et. al.). This study, using a human ex vivo uterine perfusion model, was published in Human Reproduction in 1997. Thirty-nine hysterectomy specimens were studied where tritium-labeled and unlabeled progesterone was applied to the cuff of the vaginal tissue. In addition, carbon-14 dextran was also used to study nonspecific transport or leakage, which may

occur using this model. After exposure at various time methods, they prepared sections of uterine tissue, which were exposed only to the tritiated progesterone. What they found was that a steady state was achieved after 4 hours, meaning that the tritiated progesterone was found at its maximum concentration in the uterus after 4 hours. When sampling various locations of the uterus over time, they found that tritiated progesterone was fully integrated throughout the uterus, both endometrium and myometrium (even in the fundus), after 4 hours. This was ultimately called the first uterine pass effect.

There are three different hypotheses which have been reported to explain this: (1) direct diffusion through or between cells to the vagina to the uterus, (2) portal-like arrangements of lymphatics linking the upper vagina to the uterus, and (3) a counter occurrence circulation system, much like a portal system, with vein to artery diffusion between the upper vagina and uterus.

### C. Crinone, a New Progesterone Product

#### 1. Bioadhesive Properties

Columbia Research Laboratories developed a bioadhesive vaginal gel called Crinone. Crinone is a progesterone which has a polycarbophil polymer base. The polycarbophil polymer confers bioadhesive properties to the gel, which allows the gel to stick to the vagina. Unlike typical vaginal suppositories which need to be administered twice daily, Crinone has a longer sustained release of progesterone and, therefore, allows once a day administration. Crinone has a half-life of 35 hours. There is direct transport to the target organ, namely the uterus, which maximizes the endometrial effects while minimizing the effects of drowsiness. We seen this product before; Replens is a polycarbophil based moisturizing system. The applicator for Replens is similar to that for Crinone. The actual medication is < 2 gms. The polycarbophil mimics mucin, has a negative charge physiologically which allows it to mimic mucin and adhere to the vaginal wall.

#### 2. Dose Effect

Columbia Research Laboratories supported another study where three different doses of Crinone were used: 45 mg, 90 mg and 180 mg for women undergoing an egg donor mock cycle. Endometrial biopsies were performed on Day 20 and Day 24. They found that in all cases, in-phase endometrium was found where secretory transformation occurred in the glands and adequate decidualization occurred in the stroma.

#### 3. Oocyte Donation Model

Armed with this knowledge, Dr. Gibbons conducted a study using oocyte donation patients. There were 99 women with premature ovarian failure between the ages of 28 and 47 who were prepared using estradiol patches and received either progesterone gel, 90 mg twice daily, or intramuscular progesterone 100 mg daily. During a test cycle, what they ultimately found was that the pregnancy rates were not statistically different, nor were the delivery rates. Dr. Gibbons and Dr. Toner are currently using the Crinone in a once a day regimen in an on-going study.

#### 4. UT Southwestern Crinone IVF Study

We are currently using Crinone with our IVF luteal phase support instead of intramuscular progesterone in all of our homologous IVF patients. We have measured serum progesterone in the midluteal phase and have found that all of our patients have had serum levels of >10 ng/mL. So far, our pregnancy rates have not differed when using Crinone compared to intramuscular progesterone. This study is ongoing.