The Use of Isomolecular Progesterone in the Support of Pregnancy and Fetal Safety

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Introduction

Progesterone support in pregnancy has been in use for over 60 years, having received its start in the 1940s. Its initial use was in patients who had habitual spontaneous abortion caused by luteal phase deficiency. More recently, the administration of progesterone later in pregnancy has been considered to be justified because of an observed decrease in circulating progesterone with the onset of labor,[1] an association of premature labor with decreased progesterone concentrations,[2] and the observation that progesterone has a tocolytic effect.[3]

A considerable boost to the use of progestational agents to reduce preterm delivery was received with the publication of two papers which showed a sigificant reduction in preterm delivery rates with the prophylactic administration of either progesterone or 17-*a* hydroxyprogesterone caproate. Recently it has been shown, however, that its use is not universal.[4] This may be related to the significant late sequelae that were documented following the *in utero* exposure of the fetus to the potent steroid diethylstilbestrol (DES) and that this bad experience cast "a long shadow,"[5] In spite of this, the use of proges-

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[1] Turnbull A, Patten P, Flynt A, Keirse J, Jeremy J, Anderson A: Significant Fall in Progesterone and Rise in Estradiol Levels in Human Peripheral Plasma Before Onset of Labor. *Lancet* 1974; i:101.

[2] Csapo A, Pohanka O, Kaihola H: Progesterone Deficiency and Premature Labour. *Br Med J* 1974; i:137.

[3] Ferre F, Usan M, Janssen SY: Oral Administration of Micronized Natural Progesterone in Late Human Pregnancy: Effects on Progesterone and Estrogen Concentrations in the Plasma, Placenta and Myometrium. *Am J Obset Gynec* 1985; 148:26.

[4] Ness A, Dias T, Damus K, et al: Impact of the Recent Radomized Trials on the Use of Progesterone to Prevent Preterm Birth: A 2005 Follow-up Survey. *Am J Obstet Gynec* 2006; 195:1174.

[5] Green MF: Progesterone and Preterm Delivery – Déjà Vu All Over Again. *N Engl J Med* 2003; 348:2453.

terone, at least in early pregnancy, is widespread in the various artificial reproductive programs and is growing in its use as an agent to reduce prematurity.

Over the years, there has been an extraordinary amount of confusion related to the use of progesterone support in pregnancy. The Food & Drug Administration (FDA) created some of this confusion. In various labeling of progesterone products by the FDA, one of the contraindications to the use of oral progesterone is listed as "known or suspected pregnancy."[6] And, yet, no such contraindication is identified for the use of progesterone gel. In fact, progesterone gel is indicated for progesterone supplementation or replacement as a part of an assisted reproductive technology (ART) treatment program for infertile women with a progesterone deficiency.[7] To make this even more confusing, oral progesterone, while it was contraindicated in "known or suspected pregnancy," its official labeling stated that it "should be used during pregnancy only if indicated (see contraindications)." Also, up until very recently, there was a dire "warning" contained in the labeling for USP progesterone injection in sesame seed oil regarding an increased possibility of birth defects.[8] An analysis of the fetal safety of isomolecular progesterone (Pregn-4-ene-3,20-dione) administration during the course of 1,310 pregnancies over a 35-year period of time (1979-2014) was undertaken to address this confusion.

Methods

All of the patients who were involved in this study were patients of the Pope Paul VI Institute for the Study of Human Reproduction. This is a Catholic program for the evaluation and treatment of reproductive disorders. There were 2,732 pregnant patients who made up the initial study population. Of these, 2,094 received progesterone during the course of their pregnancy and 638 did not. However, 667 of those pregnancies were cared for in other geographic locations by physicians not associated with the Institute and it was thought that followup with those patients was not adequate to utilize as part of this study. This left 2,065 patients who were cared for by the authors or other physicians at the Pope Paul VI Institute. Of these, 1,763 were 20.0 weeks of gestation or greater at the time of delivery. In that group, 1,310 pregnancies were supported by progesterone and 453 were not. This obstetrical practice has been a generally high-risk reproductive medicine/infertility population and made up the study and comparison group for this analysis.

The mean level of progesterone during the course of pregnancy on an every 2-week basis from 4 to 40 weeks gestation was identified along with 1 standard deviation away from the mean. The different segments of the curve were then divided into Zones 1,2,3 and 4. The indications for progesterone monitoring and supplementation included the following: the previous occurrence of one of the following – spontaneous abortion; infertility; stillbirth; prematurity (<37 weeks gestation); premature rupture of membranes

[6] Physicians Desk Reference (PDR), 57th Edition, Thomson PDR, Montvale, NJ 2003 pp. 3166.

[7] Physicians Desk Reference (PDR), 57th Edition, Thomson PDR, Montvale, NJ 2003 pp. 3121.

[8] Progesterone Injection, USP in sesame oil. Watson Pharma Inc., Product Literature, Morristown, NJ 2001.

(<37 weeks gestation); pregnancy-induced hypertension; or abruption of the placenta. A congenital uterine anomaly, a patient who received a cervical cerclage and/or patients who simply had a low progesterone during the early course of their pregnancy were also considered candidates for progesterone supplementation.

During the course of these pregnancies, progesterone was administered using progesterone in sesame seed oil either 100 mg or 200 mg intramuscularly every 3-4 days during the course of the pregnancy, and the maternal serum progesterone level was monitored every two weeks. The first progesterone level was drawn usually 16-18 days after the estimated time of conception. Conception was estimated using the Peak Day observation of the **CREIGHTON MODEL FertilityCare™ System** which was charted by most of these patients in this study. This day has been shown to be closely associated with the time of ovulation (+/- 2 days in 95.4% of cycles[9]).

In cases where the patient was not using the **CREIGHTON MODEL System** the pregnancy was dated by the use of the ultrasound measurement of the crown rump length or gestational sac obtained generally between the 6th and 9th week of pregnancy. The progesterone levels were drawn every 2 weeks prior to an injection of progesterone –72 to 96 hours following the previous progesterone injection – at the expected *trough* of the exogenously administered progesterone. In the evaluation of the normal progesterone curve during the course of pregnancy, it was found that there was virtually no difference in the progesterone curve between a normal primigravid and a normal multigravid pregnancy (this is described in detail elsewhere[10]).

The first patient who received progesterone received it in 1979 and this study is a compilation of all of the pregnancies in patients who received progesterone and were delivered through the physicians at the Pope Paul VI Institute through 2014. Beginning in 1985, an extensive chart review was begun for each of the pregnancies. Each record was individually reviewed including the prenatal form, all documentation of the delivery, any notes in the chart at the time of delivery, at the postpartum examination or in the nursing notes were evaluated and recorded. All letters regarding the health of the newborn that were provided by the pediatrician or family physician were also reviewed. This recording took into account the following factors: the age of the patient, geographic home location, gravidity and parity, the number of previous spontaneous abortions and any other reproductive history that might be important. In addition, the gynecologic history, pregnancy number, fetal age at the first visit, estimated date of delivery, the pregnancy outcome, gestational age at outcome and birth date were also recorded. Additional items included whether the delivery was vaginal or Cesarean section, a single or a multiple pregnancy, whether the patient had a cerclage or not, whether she developed toxemia, had a previous induced abortion, previous infertility, a placenta previa and/or premature rupture of membranes. Furthermore, the development of fetal

[9] Hilgers TW, Abraham GE, Cavanagh D: Natural Family Planning – I. The Peak Symptom and Estimated Time of Ovulation, *Obstet Gynecol* 1978; 52:575.

[10] Hilgers TW: Assessing Progesterone during Pregnancy. In: Hilgers TW: The Medical and Surgical Practice of NaProTECHNOLOGY. *Pope Paul VI Institute Press* 2004, pp 713ff.

distress in labor was recorded, the presence of postpartum depression, chronic hypertension, adherent placenta, postpartum bleeding, placental abruption, the presence of fetal anomalies and what that anomaly was, the use of progesterone in the pregnancy, the use of terbutaline or any other tocolytic and IV antibiotic use were all recorded. In addition, in many of the pregnancies, the Apgar scores were also identified. This review of the record was then made on an every 2-year basis to compile the record for which this long-term study was accomplished.

In addition to that, there was a subgroup of 686 patients who were reviewed for the total amount of progesterone given to them during the course of their pregnancy and what the route of administration was (intramuscular, oral or vaginal). This was then recorded and evaluated. Some patients received intramuscular progesterone only (n=496, 72.3%) while others received only oral progesterone (n=10, 1.5%) or only vaginal progesterone (n=13, 1.9%). A combination of 2 or more of these routes of administration occurred in 167 patients for a total of 24.3%. At all times, isomolecular or bioidentical progesterone (Pregn-4-ene-3,20-dione) was used.

Results

The age, gravidity, parity, history of infertility and mean number of previous miscarriages was recorded for those patients who were on progesterone and compared to those who were not on progesterone. The patients who took progesterone were, on average, older (29.9 vs 26.3 years), had had more pregnancies (3.2 vs. 2.6), a more prominent history of infertility (45.2% vs. 12.7%) and the mean number of spontaneous abortions was larger in the group who had taken progesterone (0.8% vs. 0.3%). These were all in the highly significant range. Parity was basically the same between the 2 groups.

In a large subgroup of those patients (n=686) who received progesterone by the intramuscular route (n=661), the average total amount of progesterone they received during the entire course of the pregnancy, was 4,961.2 mg. For those who received oral progesterone (n=142), they received 37,245.8 mg of progesterone during the course of their pregnancy, and those who received vaginal progesterone (n=59) received a total of 67,769.5 mg (Table 2). The differences between the different groups are a representation of the different absorption capabilities of the different routes of administration with the absorption of progesterone through the intramuscular route being the highest and most rapid.

The various fetal anomalies that were observed, both in those patients who took progesterone (n=1,310) and those who did not take progesterone (n=453) is shown in Table 1. The total number of anomalies observed in those taking progesterone was 29 (in 1,310) for an incidences of 2.2%. The total number of anomalies observed in those who did not take progesterone was 10 (in 453) for an incidences also of 2.2%. By Chi-square analysis, this is not statistically significant (p=0.99). Looking at the individual anomalies, there was no statistically significant difference between those that were on progesterone and those that were not on progesterone for any of the anomalies identified.

Table 1

Specific Fetal Anomalies Observed in Patients On Progesterone (n = 1,310) vs. Those not on Progesterone (n = 453)

Pope Paul VI Institute for the Study of Human Reproduction (1979 – 2014)

Anomaly Observed	On Progesterone (n = 1,310) n	%	Not On Progesterone (n = 453) n	%	P Value
Down syndrome	5	0.4	0	0.0	0.19[1]
Cardiac anomaly	4	0.3	1	0.2	0.77[2]
Trisomy 13	3	0.2	1	0.2	0.97[3]
Cleft lip/palate	3	0.2	1	0.2	0.97[3]
Other chromosome Anomalies	2	0.2	1	0.2	0.76[4]
Polydactyly	2	0.2	0	0.0	0.41[5]
Renal anomalies	1	0.1	1	0.2	0.43[6]
Omphalocele / BW	1	0.1	1	0.2	0.43[6]
Imperforate anus/ club foot/ectopic anus	2	0.2	0	0.0	0.41[5]
Aqueductal stenosis	1	0.1	0	0.0	0.56[7]
Labial fusion	1	0.2[8]	0	0.0	0.57[8]
Hypospadias	1	0.2[9]	0	0.0	0.53[9]
Wilms tumor	1	0.1	0	0.0	0.56[7]
Rhabdomyoma of Heart	1	0.1	0	0.0	0.56[7]
Wiskott Aldrich Syndrome	1	0.1	0	0.0	0.56[7]
Dandy Walker Malformation	0	0.0	1	0.2	0.089[10]
Pyloric stenosis	0	0.0	1	0.2	0.089[10]
Tracheal atresia	0	0.0	1	0.2	0.089[10]
UPJ Obstruction	0	0.0	1	0.2	0.089[10]
Total	29	2.2	10	2.2	0.99[11]

1 = Chi-square analysis (Chi-square = 1.727,1)
2 = Chi-square analysis (Chi-square = 0.0848,1)
3 = Chi-square analysis (Chi-square = 0.0010,1)
4 = Chi-square analysis (Chi-square = 0.0915,1)
5 = Chi-square analysis (Chi-square = 0.6914,1)
6 = Chi-square analysis (Chi-Square = 0.6176,1)
7 = Chi-square analysis (Chi-square = 0.3458,1)
8 = Based upon 549 females exposed to progesterone and 218 not exposed, Chi-square analysis, (Chi-square = 0.3976,1)
9 = Based upon 570 males exposed to progesterone and 226 not exposed, Chi-square analysis (Chi-square = 0.3970,1)
10 = Chi-square analysis (Chi-square = 2.887,1)
11 = Chi-square analysis (Chi-square = 6.049e-005,1)

Many of the anomalies that were identified were chromosomal in nature and would have occurred at the time of conception and would not be associated with any drug taken after pregnancy occurred. There were more chromosomal anomalies in those who

took progesterone (n=14, 1.1%) than those who were not on progesterone (n=3, 0.7%). However, the difference is not statistically significant (p=0.45, Chi-square analysis). The number of non-chromosomal anomalies in those taking progesterone was lower (n=15, 1.1%) than those who were not on progesterone (n=7, 1.5%). These would be the anomalies that might be related to a teratogenic effect of a particular medication, but again, there was no statistically significant difference (p=0.51, Chi-square analysis).

The most frequent route of administration was intramuscular progesterone and it was often given in this particular population of patients into the 2nd and 3rd trimesters of pregnancy. This was because the serum progesterone levels in the mother were in Zone 1 or lower Zone 2 during the course of that pregnancy into the 2nd and 3rd trimesters.

Discussion

A number of approaches to the use of progesterone support in pregnancy have been utilized over the years. These support programs are noteworthy in their lack of uniformity. The two that have generally been used are 17 a-hydroxyprogesterone caproate (17 0HP-C) and progesterone (P). It has been an edict of contemporary reproductive medicine that progesterone should not be administered after the first trimester of pregnancy. However, in this day of "evidence-based medicine," there is little evidence upon which to base this edict since progesterone levels are generally not followed.

The corpus luteum is the major source of progesterone during the first 9-10 weeks of pregnancy. There is, however a shift in progesterone production from the corpus luteum to the placenta between the 6th to the 11th week of pregnancy. During the 2nd and 3rd trimesters of pregnancy, it has generally been thought that the placenta is the major source of progesterone production. However, it has also been shown that the corpora lutea of pregnancy continues to produce progesterone during this period of time.[11] Progesterone concentrations in the peripheral vein of women at term were the same as the progesterone concentration in the ovarian vein coming from the ovary where there was no corpus luteum. The progesterone concentrations from the ovary in which a corpus luteum was present, however, were more than twice that of the progesterone levels in the peripheral vein.

In women who have preterm labor, serum levels of progesterone and 17 a-hydroxyprogesterone are significantly decreased during the 2nd and 3rd trimesters of pregnancy. Progesterone has an inhibitory effect on uterine muscle contractility. The effect of progesterone on uterine contractility may be mediated through the inhibition of prostaglandin-induced myometrial activity which is inhibited by progesterone; and, progesterone may decrease the number of gap junction formations in the myometrium. Progesterone is also found in very large concentrations in the myometrium of the pregnant uterus and that concentration can be increased further with the oral administration of micronized isomolecular progesterone. The observation that there is an increased

[11] LeMaire WJ, Conly PW, Moffett A, Cleveland WW: Plasma and Progesterone Secretion by the Corpus Luteum of Term Pregnancy. *Am J Obstetrics Gynec* 1970; 108:132.

frequency of uterine contractions associated with an increased likelihood of preterm delivery is further evidence of the important association of these findings.

For over 35 years, the senior author has been supplementing pregnancies with progesterone. This project began with the use of progesterone in early pregnancy in patients with infertility or a previous history of miscarriage. The initial goal of progesterone therapy was to decrease the incidence of miscarriage in subsequent pregnancies.

As this project began to grow, it was difficult to determine the dosage of progesterone that should be given and an objective means by which the pregnancy could be monitored. This led to the measurement of serum progesterone levels during the course of pregnancy. Eventually, a standard curve for progesterone in pregnancy (a normogram) was developed and the ability to objectively assess progesterone became possible (this is explained in detail elsewhere).

The Pope Paul VI Institute Progesterone Support Program has several important features to it:

1. First and foremost, is its ability to objectively monitor the dose of progesterone being provided based upon the serial monitoring of serum progesterone levels during pregnancy.
2. Its selection of progesterone over the use of 17 *a*-hydroxyprogesterone caproate (17-0HP-C).
3. Its use during the course of pregnancy where supplementation can be objectively quantified. Thus, it is not limited to the use in only the first trimester of pregnancy but often extends into the 2nd and 3rd trimesters.
4. Its proven safety.

Progesterone has been selected as the hormone of choice for the support of pregnancy over and above 17 *a*-hydroxyprogesterone caproate (17-0HP-C). 17 *a*-hydroxyprogesterone hexonate (17-0HP-H) or medroxyprogesterone acetate (MPA). The selection of isomolecular progesterone was based upon the following factors:

1. Isomolecular progesterone (Pregn-4-ene-3,20-dione) is the main natural support hormone of pregnancy.
2. 17-0HP-C, 17-0HP-H and MPA are all synthetic analogs of 17-alpha hydroxyprogesterone and progesterone and are thus chemically different from natural progesterone. This likely decreases their ability to bind to myometrial progesterone receptors.
3. 17-0HP-C, which is most commonly used and the subject of one of the recent revival papers, was manufactured under the trade name Delalutin (Bristol-Myers-Squibb Company), but its manufacture was discontinued in 1986 due to declining sales. It has been available through compounding pharmacies and, most recently, has once again appeared commercially but it is extraordinarily expensive in its commerical form.
4. While 17-0HP-C can be considered safe in pregnancy (as is progesterone), MPA has still a few lingering questions remaining with regard to safety.

5. Progesterone is a completely natural hormone. That is, it is a hormone manufactured in abundance by the human body during pregnancy while the others are all foreign to the body and not manufactured by it.

The key to the objective supplementation of progesterone during pregnancy is the availability of a meaningful standard curve (or normogram) for the production of progesterone during the course of pregnancy. These curves are not available in most laboratories. The National Women's Hormone Laboratory of the Pope Paul VI Institute, however, has developed such a curve in the many years of its work in the use of progesterone-supported pregnancy. The standard curves for normal pregnancy have been worked out using radioimmunoassay procedures and chemiluminescence technology.

During the course of pregnancy, progesterone levels are drawn on an every 2-week basis, and progesterone is supplemented based upon the progesterone level. The dosage of progesterone administered is determined based upon the zone that the progesterone level is in.[10] When the progesterone level is drawn, it is always drawn immediately prior to the administration of the subsequent progesterone dose. In this way, the progesterone level is drawn at the bottom of the natural absorption pattern of the exogenously administered progesterone and is thus drawn at its trough. In this way, a best estimate of the baseline production of progesterone during the course of that pregnancy can be obtained and an objective decision can be made relative to the next dosage of progesterone to be administered. The goal of treatment is to see that the serum progesterone level during pregnancy reaches either the mean level or is in Zone 3 or Zone 4.

Green has pointed out that the problems identified with the use of diethylstilbestrol (DES) has cast "a long shadow" on the use of hormonal supplementation in pregnancy.[5] In addition, there appears to be an extraordinary amount of confusion related to the use of progesterone support in pregnancy. Furthermore, the Food & Drug Administration (FDA), which is quite capable of relieving this confusion, has instead continued the confusing story and some of this needs to be addressed.

Much of the confusion surrounds a user-unfriendly nomenclature as it specifically relates to progestational agents. The term "progesterone" is often used loosely to refer to any progestional agent including both C21 and C19 agents. But progesterone is progesterone and nothing more. It is produced naturally in the human body along with other naturally-occurring progestational agents such as 20 alpha-dihydroprogesterone, 20 beta dihydroprogesterone, and 17 *a*-hydroxyprogesterone. Progesterone is the only known natural progestational agent with major biologic signficance and 17 *a*-hydroxyprogesterone is virtually inert. A new nomenclature has been suggested in an attempt to clarify these difficulties. Those progestational agents which are natural to the human body, i.e., are actually manufactured physiologically within the body, are best referred to as isomolecular hormones (IMH) and by their specific name. Those pregestational agents which are artificial to the body, i.e., are not manufactured physiologically in the body, are best referred to as heteromolecular artimones (artificial substitutes for naturally-occurring hormones). In this way, one can begin to distinguish between those

compounds which are naturally occurring to the body and which are foreign to it. This becomes important as one looks at the overall question of safety. IMH progesterone is a C21 steroid deriving from the pregnane nucleus. There are certain HMA artimones that are also C21 compounds. These include 17 *a*-hydroxyprogesterone caproate (17-0HP-C) and medroxyprogesterone acetate (MPA).

There are also C19 steroids derived from the androstane nucleus. Testosterone is the prototypical C19 steroid. While testosterone is a naturally-occurring C19 steroid with obvious androgenic properties, there are a number of artificially-derived C19 compounds which are less androgenic, but also have progestational activity. These include compounds such as norethindrone (19-norethinyltestosterone), norethynodrel, norgestrel, and ethisterone (ethinyl testosterone). These 19-nortestosterone derivatives unequivocally can masculinize the female fetus if given in high doses at susceptible times of embryogenesis.

The effect of these 19-norcompounds was recognized by Wilkins and Jones, et al, in 1958 and this study continues to be cited as a cause for confusion. This study, from Johns Hopkins University, presented 21 cases of females that showed evidence of masculinization of the external genitalia. In 12 of these cases, there was *in utero* exposure primarily to the C19 artimone, ethisterone (ethinyl testosterone). In 3 cases, no steroids were used in pregnancy and in the remaining 6 cases, IMH progesterone was used. However, of those 6 cases, 3 were also exposed to ethisterone and one to methyltestosterone, explaining the defect. In the other cases, the women also received stilbestrol. There is evidence that this can also exert a masculinizing influence.

In an extensive review of the fetal effects of progestational agents (both natural and artificial), Simpson and Kaufman concluded that despite many cohort and case-controlled studies, there still remains little reason to suspect that progesterone exposure *in utero* exerts a deleterious effect on fetal development. The exceptions are the 19-nortestosterone derivatives, which in high does (10-20 mg daily) can cause genital virulization.[12] They concluded that the evidence is considerable that progesterone does not cause a general increase in birth defects, are not cardiac teratogens, do not cause limb reduction defects, do not cause neural tube defects or hydrocephalus and the frequency of esophageal atresia has not been increased in any of the studies and *in utero* exposure is unlikely to result in abnormal development of the male genitalia. Other reviews have come to similar conclusions.

With the experience presented in this report, the incidence of fetal anomalies in patients on progesterone was 2.2% versus those who were not taking progesterone (2.2%). The difference is not statistically significant (p=0.99 - Chi square analysis). We observed one male infant with hypospadias with an incidence of less than 0.1%. This is significantly lower than the quoted incidence of 5-8/1,000 (0.5-0.8%), and even more signficantly different than the claim that progesterone may be associated with doubling of

[12] Simpson JL, Kaufman RH: Fetal Effects of Estrogens, Progestogens and Diethylstilbestrol. In: Fraser IS, Jansen RPS, Lobo RA, Whitehead MI: Estrogens and Progestogens in Clinical Practice. *Churchill Livingstone, London* 1998, pp. 533-553.

that frequency. It was also observed that one female infant had mild labial fusion treated effectively with estrogen cream (incidence of 0.1%). But this, too, is much lower than the reported incidence of 1.8%. In both cases, there was no significant difference in the incidence between those on progesterone versus those who did not take progesterone.

This series of patients is the largest database on the use of progesterone that has ever been reported for isomolecular (bioidentical) progesterone supplementation in pregnancy. Furthermore, nearly all of these patients had exposure to progesterone during the first 4 months of pregnancy and no increase in any of the anomalies was observed.

It was observed that the incidence of Down syndrome was more common in the group that received progesterone than those that did not (however, it was not a statistically significant increase). Because the number of patients in the progesterone group who had a previous history of infertility and more previous spontaneous abortions, it is suggested that this increased incidence might be related to that previous history. In both cases, the number of anomalies in the progesterone versus the non-progesterone group, whether they were chromosomal or non-chromosomal was not significantly different from those that were not on progesterone.

In conclusion, specifically as it relates to the naturally occurring hormone progesterone (Pregn-4-ene-3,20-dione), there is no credible evidence to suggest that if it is used to support pregnancy, that it is teratogenic or responsible for genital malformations. This is true whether that support is in the early days of pregnancy or later in pregnancy.