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PROGESTERONE USE IN PREGNANCY VALUABLE TO REDUCE MISCARRIAGES AND PRETERM DELIVERIES

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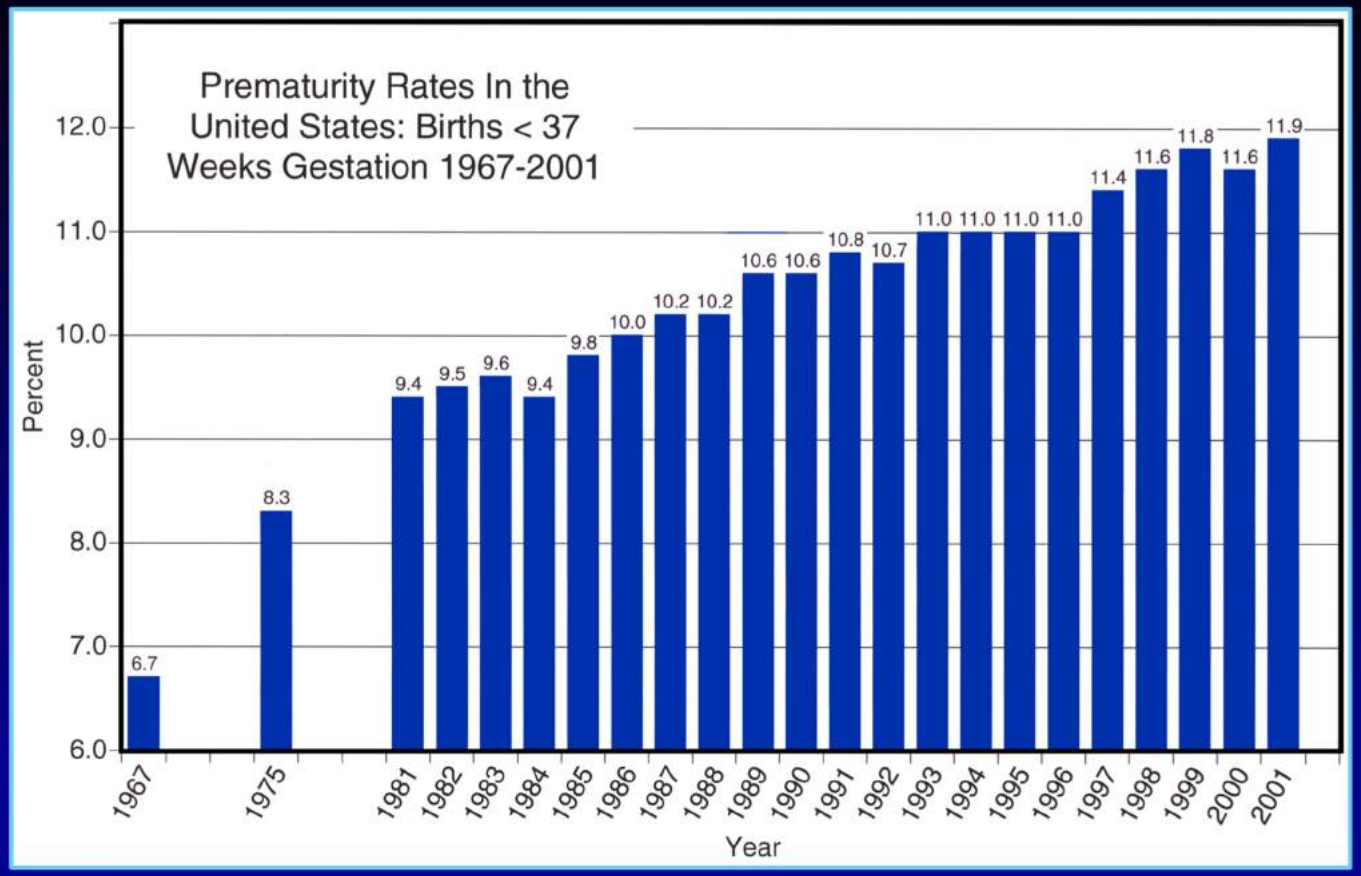


The prematurity rate in the United States (birth less than 37.0 weeks gestation) 1967-2001.[1-4]

Summary of Medical and Developmental Problems Associated with Premature Birth

Medical

- Responsible for 70% of fetal, neonatal and infant deaths
- Increased rates of intraventricular hemorrhage
- Increased risks of respiratory distress
- Increased risk of cerebral palsy, and visual and hearing impairment

Developmental

- Abnormal cognitive function
- Abnormal academic skills
- Poor visual motor function
- Poor gross motor function
- Poor adaptive function
- Mental retardation and developmental delay

Prematurity Prevention Program of the Pope Paul VI Institute

1. Identify patients who are at high risk
2. Uterine contraction self-monitoring (patient education)
3. Supplement with IM progesterone while monitoring serum levels
4. Tocolytic therapy (usually Terbutaline) for symptoms of uterine irritability (contractions)
5. Antibiotic therapy when patient breaks through tocolytic therapy
6. Ultrasound assessment of cervix when dictated by risk criterion, symptoms or pregnancy condition
7. Cerclage when indicated by ultrasound assessment

Summary Table of Statistically Significant Changes in Progesterone Levels by Condition or Event

Condition or Event	Trimester First	Second	Third
Previous History			
PCOD	↓	↓	↓
IAB	NC	↓	↓
One SAB	NC	↓	↓
Three or more SAB	NC	↓	↓
Prematurity	NC	↓	↓
Current Pregnancy			
First Trimester SAB	↓	--	--
Second Trimester SAB	↓	↓	--
Adherent placenta	↑	↓	NC
Low lying placenta & placenta previa	NC	↓	↓
Midtrimester abruption	NC	↓	↓
Terbutaline only	↑	↓	↓
Antibiotic RX	NC	↓	↓
PROM	NC	↓	↓
Cerclage	NC	↓	↓

↓= statistically significant decrease

↑= statistically significant increase

NC = no change

Higgins TW. **The Medical & Surgical Practice of NaProTechnology** Pope Paul VI Institute Press, Omaha, NE. 2004.

Summary Table of Statistically Significant Changes in Progesterone Levels by Condition or Event (cont'd)

Condition or Event	Trimester First	Second	Third
Current Pregnancy			
Twins	↑	↑	↑
Postpartum depression	↑	↓	NC
Toxemia	↑	NC	NC
PIH	NC	↓	NC
Smoker	NC	↓	↓
Postpartum hemorrhage	NC	↓	↓
Meconium stained AF	↑	↓	NC
Fetal distress	NC	↓	↓
Low Apgars	NC	↓	↓
Low BPP	NC	↓	↓
IGR	NC	↓	↓
Oligohydramnios	NC	↓	↓
Groups			
Abnormal placentae	↑	↓	↓
Threatened prematurity	NC	↓	↓
Fetal distress	NC	↓	↓

↓= statistically significant decrease

↑= statistically significant increase

NC = no change

Hilgers TW. **The Medical & Surgical Practice of NaProTechnology** Pope Paul VI Institute Press, Omaha, NE. 2004.

Role of Ovarian Steroids

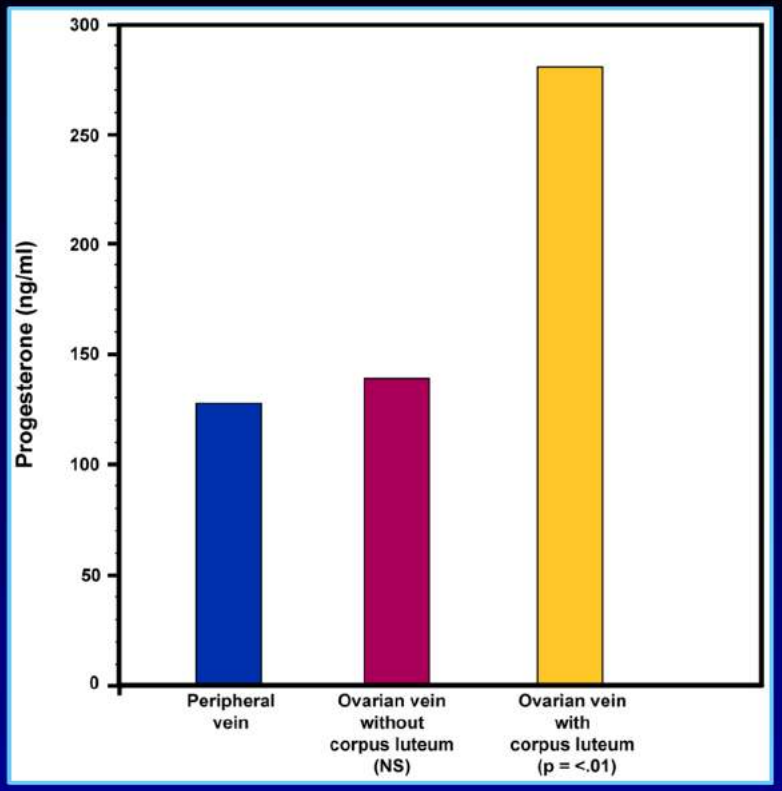
- It stimulates the growth of the uterus.
- It causes “maturation” (i.e. differentiation) of the endometrium converting it to a secretory type.
- It stimulates the decidualization of the endometrium required for implantation.
- And it inhibits myometrial contractions.

Little AB, Billiar RB: Progestogens. In: Fuchs F, Klopper A (Eds.) Endocrinology of pregnancy. 3rd Edition, Harper and Row, Philadelphia 1972, p. 92-111. From: Hilgers TW: The Medical and Surgical Practice of NaProTechnology. Pope Paul VI Institute Press, Omaha, Nebraska, 2004. Chapter 55.

Metabolic and Other Effects of Progesterone

- Does not affect the beneficial effects of estrogen on either HDL-C or LDL-C profiles
- Undergoes rapid first-pass metabolism
- Is bound to albumin and cortisol-binding globulin (CBG or transcortin)
- Has short half-life
- Metabolized in the liver primarily to hydroxylated metabolites and their sulfate and glucuronide conjugates, which are eliminated in the urine
- Has anxiolytic effects in CNS

Adapted from: Loose-Mitchell DS, Stancel GM: Estrogen and Progestins. In: Hardman JE, Limbird LE, Gilman AG (Eds). Goodman and Gillman's The Pharmacological Basis of Therapeutics. Intl Ed. (10th) McGraw-Hill; New York 2001.



Plasma progesterone levels in the peripheral vein and the ovarian veins with and without a corpus luteum in pregnancy at term (Adapted from: LeMaire WJ, Conly PW, Moffett A, Cleveland WW: Plasma Progesterone secretion by the corpus luteum of term pregnancy. Am J Obstet Gynec 108:132-134,1970).

Progesterone Concentrations in Various Compartments in Pregnancy

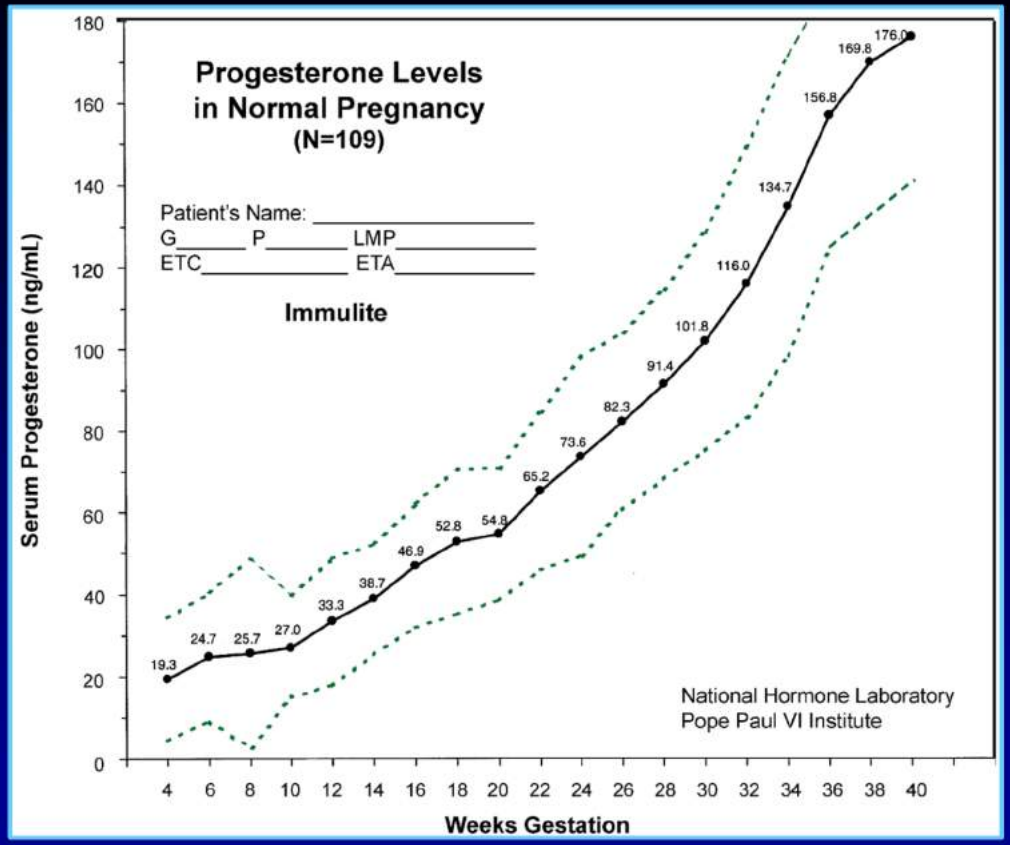
Steroid	Concentration
Maternal serum level - 10 weeks	30.0 ng/mL
Maternal serum level - 24 weeks	75.0 ng/mL
Maternal serum level - 36 weeks	153.0 ng/mL
Retroplacental blood pool	600.0 ng/mL
Fetal serum levels	7x maternal levels[3]
Progesterone production - midpregnancy	75.0 mg/day
Progesterone production - late pregnancy	250-600 mg/day
100 mg progesterone IM - peak serum level	30.3 ng/mL
200 mg progesterone IM - peak serum level	99.9 ng/mL

1. Kumar D, Barnes AC: Studies in Human Myometrium during Pregnancy. VI. Tissue progesterone profile of the various compartments in the same individual. Am J Obstet Gynec. 92: 717-719, 1961.
2. Hawkins DF: Sex Hormones in Pregnancy. In: Obstetric Therapeutics. Hawkins DF (Ed). London: Bailliere Tindall, 1974, pp. 106-141.
3. Ryan KI: Placental Synthesis of Steroid Hormones. In: Tulchinsky D, Ryan KJ (Eds): Maternal-Fetal Endocrinology, WB Saunders Co., Philadelphia, PA 1980, pp. 3-16.
4. Klopper A, Fuchs F: Progestagens. In: Fuchs F, Klopper A (Eds): Endocrinology of Pregnancy, 2nd Ed., Harper and Row, Hagerstown, M.D. 1977, pp. 99-122.
5. Pearlman WH: [16-34] Progesterone in oophorectomized-hysterectomized women. Biochem J, 67:1, 1957.

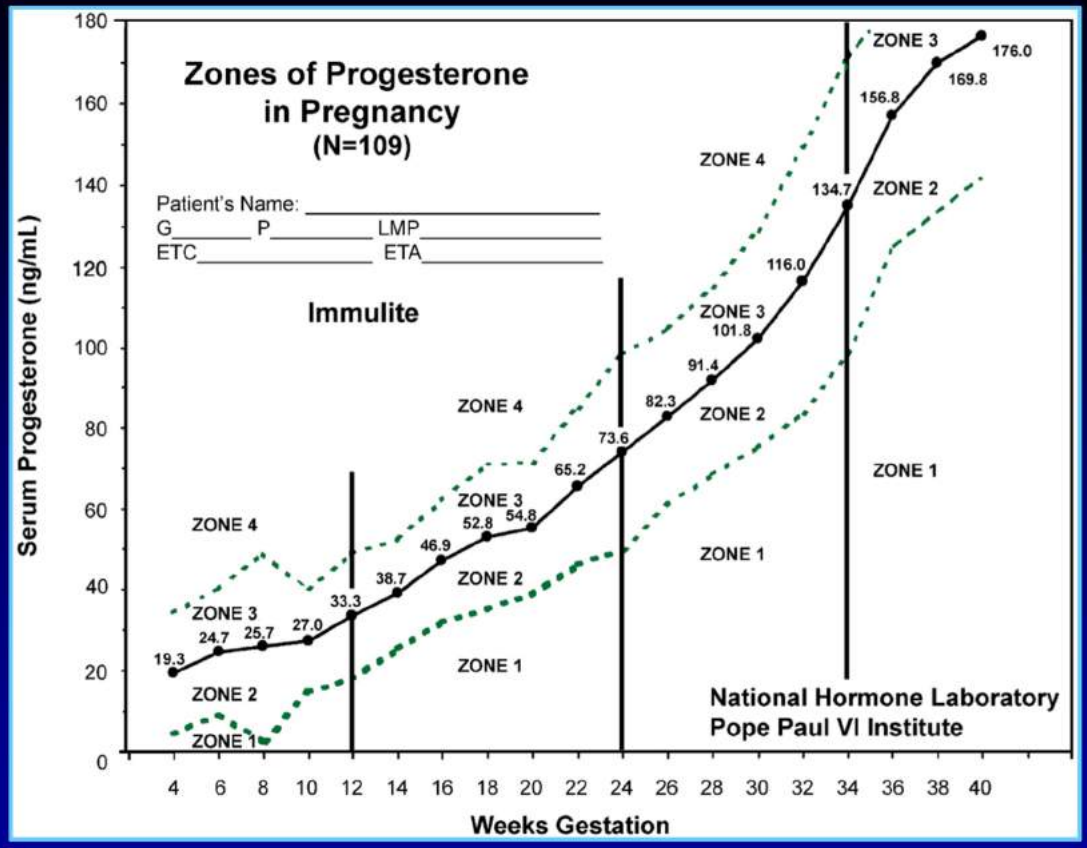
Indications of the Use of Progesterone in Pregnancy—Pope Paul VI Institute Protocol

- Previous SAB
- Previous stillbirth
- Previous prematurity (<37 weeks)
- Previous PROM (<37 weeks)
- Previous pregnancy-induced hypertension (or toxemia)
- Previous abruption of placenta
- Patient with threatened premature labor or cerclage
- Multiple pregnancy
- Infertility
- Congenital uterine anomaly (major)
- Low progesterone level

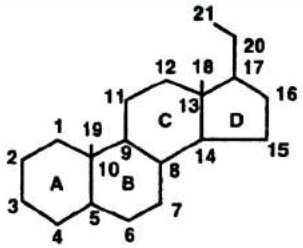
Hilgers TW. **The Medical & Surgical Practice of NaProTechnology**. Pope Paul VI Institute Press, Omaha, NE. 2004.



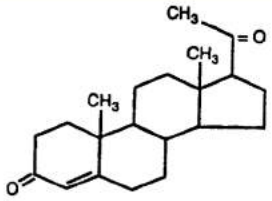
Progesterone levels in normal pregnancy with the mean and on standard deveation shown (DPC-Immulite).



The four zones of progesterone shown using the DPC-Immulite assay.

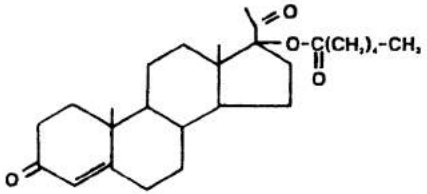


C_{21}-Steroid
(Pregnane)

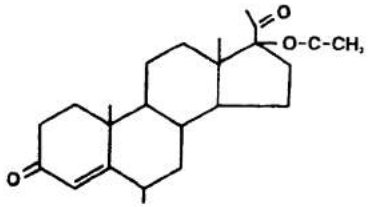


Progesterone

C-21 Progestins



Hydroxyprogesterone caproate



Medroxyprogesterone acetate

The C_{21} pregnane nucleus and the chemical structure of progesterone and the C_{21} artimones 17-OH-progesterone caproate and medroxyprogesterone acetate.

Isomolecular Hormones (IMH)

This is a chemical that is chemically (by nature of its molecular structure), biologically, physiologically and pharmacologically identical to the hormone that is manufactured naturally in the human body. While these are often referred to as “natural hormones,” the actual origin of the chemical is not as important as the isomolecular nature of it. These chemicals can be synthesized from various precursors and made to be identical to the human hormone. In fact, there are virtually no isomolecular hormones in use at the present time that are natural in the sense that they have been derived from a natural source. These hormones are also properly referred to as *bio-identical*.

Heteromolecular Artimones (HMA)

These are chemicals that are distinct and different from the isomolecular hormone to which they are often confused. In the case of reproductive hormones, they may have estrogen-like and progesterone-like activity, but invariably that activity is not the same as the isomolecular hormones. Furthermore, they also have chemical activities in the body that are distinctly different from the isomolecular hormones. These HMAs are substitutes for the "real thing." Chemical compounds with biological activities that are progesterone-like have been variously referred to in the literature as progestins, progestational agents, progestagens, progestogens, gestagens or gestogens. Often, however, the term progesterone is used to refer to these hormones and that is inaccurate. Thus, it is appropriate to refer to these substitutes as *artimones* (artificial hormones) or more specifically *HMA progestins* and *HMA estrins*.

CARBON STRUCTURE OF THESE HORMONES

PROGESTERONE IS 21 – CARBON

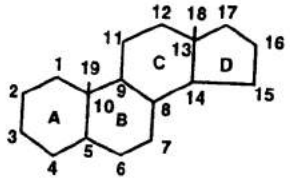
MEDROXYPROGESTERONE ACETATE (DEPO PROVERA) IS 24 – CARBON

HYDROXYPROGESTERONE CAPROATE(GESTIVA) IS A 27 – CARBON

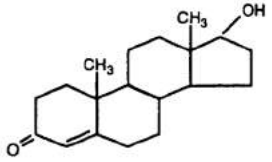
Relative Potencies of IMH Progesterone and Various HMA Progestins[1,2]

Progsterone	1
Dydrogesterone	10
Medroxyprogesterone acetate (Provera)	50
Norethindrone	500
L Norgestrel	4,000

1. The relative doses required to elicit responses similar to those seen in premenopausal, secretory endometrium.
2. Kina RJB, Whitehead MI: Assessment of the Potency of Oral Administered Progestins in Women. Fertil Steril 46: 1062, 1986.

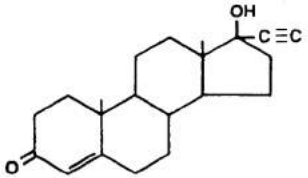


C_{19}-Steroid
(Androstane)

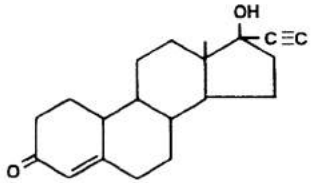


Testosterone

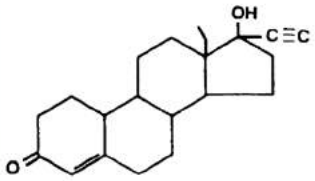
C-19 Progestins



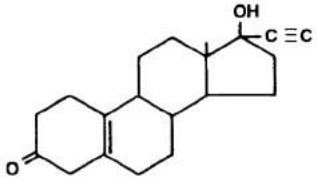
Ethinyl testosterone
(Ethisterone)



19-nor Ethinyl testosterone
(Norethindrone)



Norgestrel



Norethynodrel

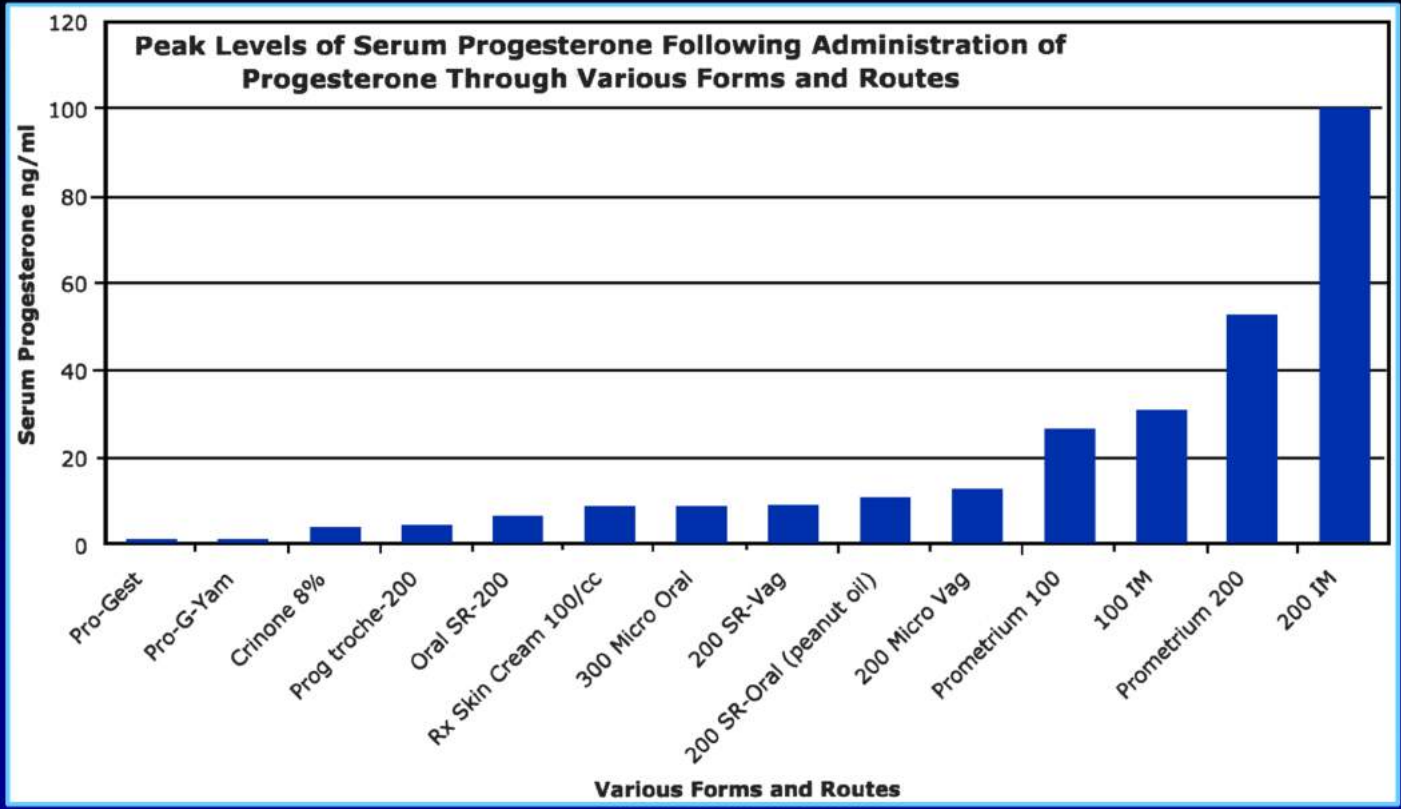
The C_{19} androstane nucleus and the chemical structure of testosterone and C_{19} artimones ethinyl testosterone (ethisterone), 19-norethinyl testosterone (norethindrone), norgestrel and norethynodrel.

Hilgers TW. The Medical & Surgical Practice of NaProTechnology
Pope Paul VI Institute Press. Omaha, NE. 2004.

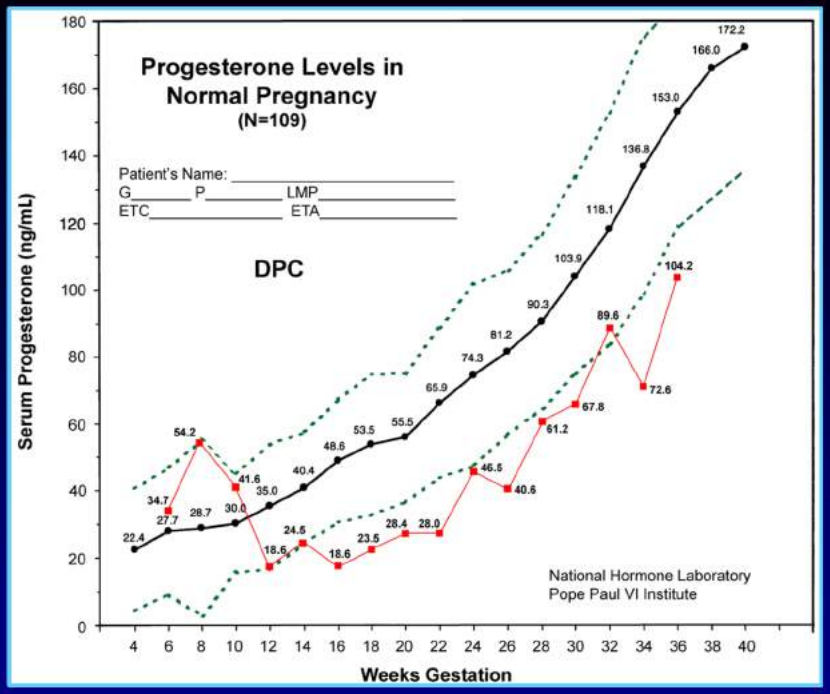
Specific Anomalies Observed in Patients On Progesterone (N= 933) vs. Not on Progesterone (N= 405)—Pope Paul VI Institute

Anomaly Observed	On Progesterone (N=933) n	On Progesterone (N=933) %	Not on Progesterone (N=405) n	Not on Progesterone (N=405) %	Published Frequency %
Renal anomaly	4	.4[a]	1	.2	.7[b]
Down syndrome	4	.4[a]	1	.2	.1[b]
Cardiac anomaly	3	.3	2	.5	.9[b]
Cleft lip and/or palate	3	.3	2	.2	.2[c]
Other chromosomal anomalies	2	.2	2	.5	.2[b]
Omphalocele	1	.1	1	.2	.03[c]
Polydactyly	1	.1	0	0	.08[d]
Club feet	1	.1	0	0	.4[c]
Labial fusion	1	.1	0	0	1.8[e]
Hypospadias	1	.1	0	0	.5 - .8[f]
GI anomaly	0	0	2	.5	.02[c]
Dandy Walker malformation	0	0	1	.2	.09[c]
Totals	**21**	**2.2[g]**	**11**	**2.7**	

a. Chi-square =0.2507 (p=.6166) when compared to those not on progesterone.
b. March of Dimes Perinatal Data Center, 2000. March of Dimes Birth Defects Foundation. www.marchofdimes.com. 2003.
C Nyberg DA, Mahoney BS, Pretorius DH: Diagnostic Ultrasound of Fetal Anomalies. Year Book Medical Publishers, Chicago, 1990, p. 22.
d. National Vital Statistics Reports. Department of Health and Human Services, National Center for Health Statistics, Feb. 12, 2002.
e. Leung AKC, Robson WLM, Tay-Uyboco J: The Incidence of labial fusion in children. J Paediatr Child Health. 29: 235-326, 1993.
f. Food and Drug Administration official labeling: Progesterone for injection, USP, in sesame oil, 2001.
g. Chi-square =0.2619 (p=.6088) when compared to those not on progesterone.

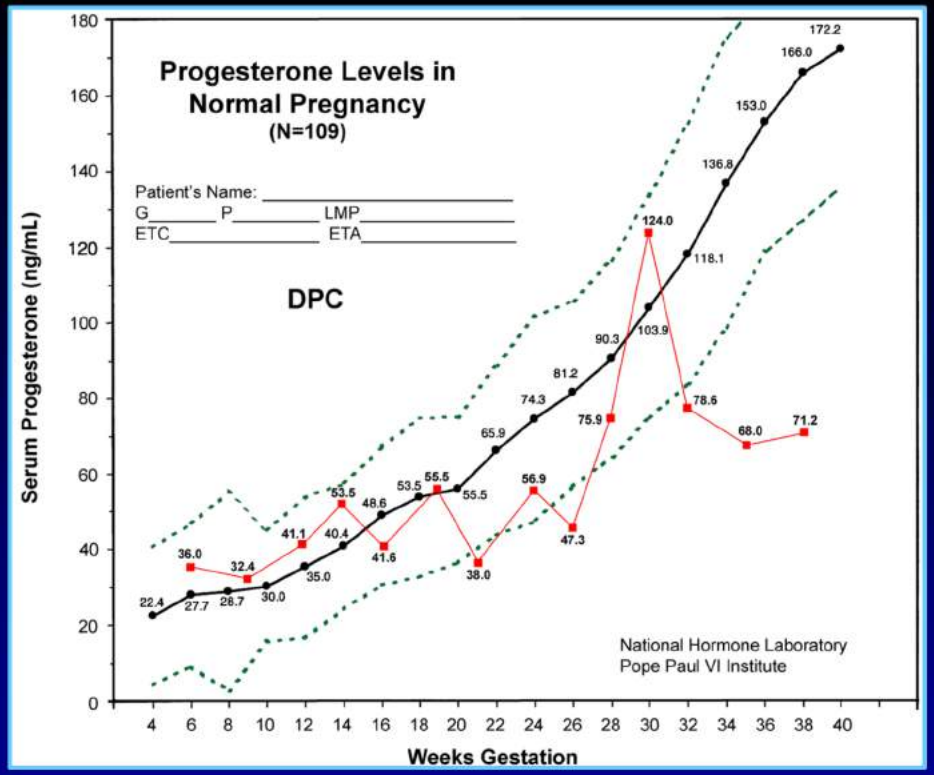


The peak levels of serum progesterone following administration of progesterone through various forms and routes.
SR = sustained release. IM = intramuscular
(From: Pope Paul VI Institute research, 2004).

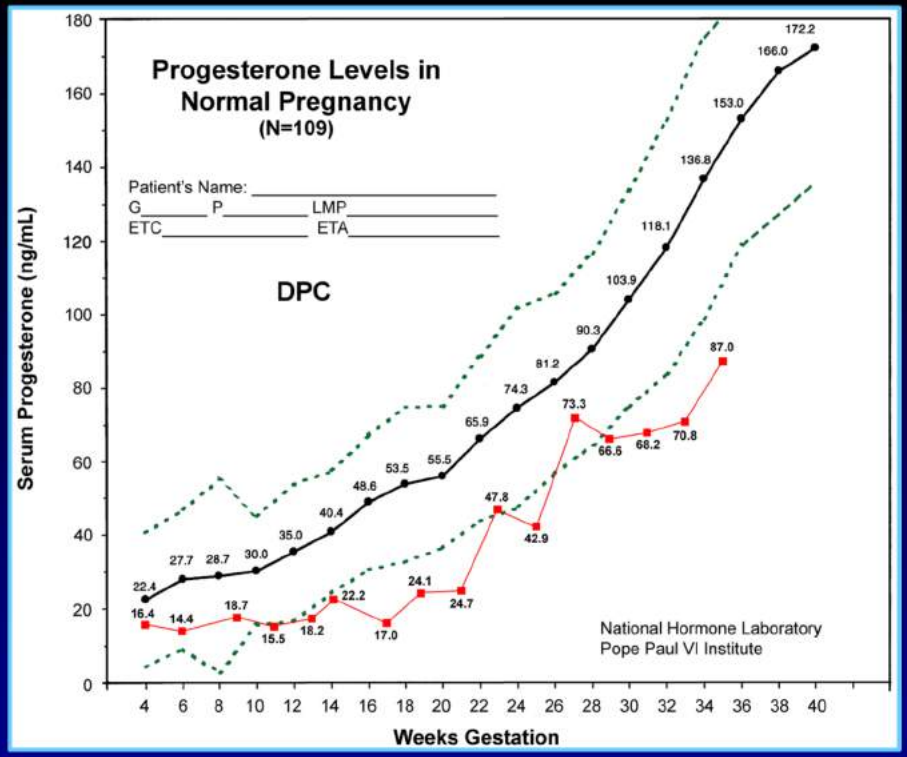


A progesterone curve of a 34-year-old, gravida 2, para 1, who had a history of having had an emergency cesarean section at term for severe fetal distress which ended in a neonatal death. She was an infertility patient with endometriosis and polycystic ovarian disease and was a heavy smoker. In the above pregnancy, her progesterone production was clearly suboptimal after looking quite favorable during the first trimester. She was supplemented with progesterone and had a healthy male infant at 38 weeks gestation by repeat cesarean section.

Hilgers TW: **The Medical & Surgical Practice of NaProTechnology**
Pope Paul VI Institute Press, Omaha, NE. 2004.



This 36-year-old, gravida 4, para 2 with one previous miscarriage developed severe IUGR during the above pregnancy. At birth, the baby weighed 4 lbs. 14 oz. She was supplemented with progesterone and her levels in the 2nd and 3rd trimester were mostly Zone 1 and lower Zone 2. **The placental weight at delivery was 197.0 grams (<10th percentile).** She delivered spontaneously at 38 weeks a small but healthy infant with Apgars of 9 and 9.



This 42-year-old gravida 1, para 1 achieved a pregnancy seven months after evaluation and treatment with NaPro**TECHNOLOGY**. Prior to coming to the Pope Paul VI Institute, she had two failed attempts at IVF. In those attempts, her endometriosis and hormone dysfunction was left undiagnosed. In her pregnancy she had a suboptimal progesterone profile usually in Zone 1 or lower Zone 2. With progesterone supplementation, she delivered a healthy female infant at 39 weeks.

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THANK YOU AND GOD BLESS