# Can Serum Progesterone Level Be Used As A Predictor Of Preterm Labor?

Thesis

*Submitted for fulfillment of Master Degree in Obstetrics & Gynaecology*

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# List of Abbreviations

| Abbrev. | Full -term |
|---|---|
| **ACTH** | **:** Adrenocorticotropic hormone |
| **ART** | **:** Assisted reproductive techniques |
| **BMI** | **:** Body mass index |
| **BV** | **:** Bacterial vaginosis |
| **CFF** | **:** Cell free fetal |
| **CI** | **:** Confidence interval |
| **CRH** | **:** Corticotropin releasing hormone |
| **DHA** | **:** Dehydroisoandrosterone sulfate |
| **DNA** | **:** Deoxyribonucleic acid |
| **FDA** | **:** Food and Drug Administration |
| **GA** | **:** Gestational age |
| **GHRH** | **:** Growth hormone-releasing hormone |
| **GnRH** | **:** Gonadotropin releasing hormone |
| **hCG** | **:** Human chorionic gonadotrophin |
| **hGH-V** | **:** Growth hormone variant |
| **hPL** | **:** Human placental lactogen |

**IL** : Interleukin

**LR** : Likelihood ratio

**OHSS** : Ovarian hyperstimulation syndrome

**P** : Protesterone

**PROM** : Preterm prelabor rupture of Membranes

**PTH-rP** : Parathyroid hormone related protein

**PTL** : Preterm labor

**P-value** : Probability value

**ROC** : Receiver operating characteristic curve

**RR** : Relative risk

**SD** : Standard deviation

**SPSS** : Statistical Package for Social Sciences

**Th** : T-helper cells

**TLR** : Toll-like receptor

**TNF** : Tumor necrosis factor

**TRH** : Thyrotropin releasing hormone

**U/S** : Ultrasound

**US** : United States

**WHO** : World Health Organization

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**Protocol of a Thesis for Partial Fulfillment of Master Degree in Obstetrics & Gynaecology**

**Title of the Protocol:**

# Can Serum Progesterone Level Be Used As A Predictor Of Preterm Labor?

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**What is already known on this subject? AND What does this study add?**

Spontaneous preterm birth is a syndrome caused by multiple etiologies, one of which is a decline in progesterone action, which induces cervical ripening. A sonographic short cervix (identified in the midtrimester) is a powerful predictor of spontaneous preterm delivery ***(Romero et al., 2013).***

This study is a trial to find a method to detect women who are more liable to develop preterm labor other than sonographic short cervix. Serum progesterone level is being tested as the method of prediction of preterm labor.

## 1.INTRODUCTION/ REVIEW

Preterm birth is defined by the WHO as birth earlier than 37 complete weeks of gestation. It continues to pose an enormous challenge in perinatal healthcare. The annual worldwide incidence of preterm birth has been estimated at around 15 million births that is, more than one in 10 babies are born preterm ***(Chang et al., 2013).***

Around one million children die each year because of complications from preterm birth such as respiratory distress syndrome, patent ductus arteriosus, intracranial hemorrhage, necrotizing enterocolitis and neonatal jaundice. Many survivors face a lifetime of disability, including learning disabilities and visual and hearing problems ***(Blencowe et al., 2012).***

The incidence of preterm birth is variably reported to be between 5 and 11% of all births and its prevention continues to remain elusive, with many reports indicating an increase in the prevalence of preterm birth in recent years ***(Dodd and Crowther, 2009).***

Many factors have been implicated, including an increase in maternal age and use of assisted reproductive techniques, resultant increase in the risk of multiple pregnancies, increasing maternal BMI, and obesity and infection ***(Leddy et al., 2008).***

Perinatal morbidity and mortality is very high in very early preterm births; however, the risk for mortality persists even in infants born between 32 and 36 weeks' gestation. Although preterm birth constitutes a relatively small proportion of total births, it is associated with more than 70% of the total perinatal mortality in developed countries, when excluding deaths related to congenital anomalies ***(Saenger et al., 2007).***

Premature birth is the major cause of hospitalization of the mother before 37 weeks of pregnancy. On the contrary it is responsible for 75% to 80% of infant mortalities. The lower the gestational age at birth, the incidence and severity of complications is higher and has a worse prognosis. Preterm birth is currently the most important problem in maternal-child health in the United States and possibly throughout the world. It accounts for over 85% of all perinatal morbidity and mortality. Although survival of preterm infants has increased steadily over the past four decades-due in large part to the use of antenatal corticosteroids, improvements in neonatal resuscitation, and the introduction of neonatal intensive care units-efforts to prevent preterm birth have been largely unsuccessful. On February 3, 2011, the US Food and Drug Administration (FDA) approved the use of progesterone supplementation (hydroxyprogesterone caproate) during pregnancy to reduce the risk of recurrent preterm birth in women with a history of at least one prior spontaneous preterm delivery. This is the first time that the FDA has approved a medication for the prevention of preterm birth, and represents the first approval of a drug specifically for use in pregnancy in almost 15 years ***(Norwitz and Caughey, 2011).***

Accumulating evidence suggests that the myometrial activity associated with preterm labor results primarily from a release of the inhibitory effects of pregnancy on the myometrium rather than an active process mediated through the release of uterine stimulants, and progesterone appears to play a central role in this regard

In the first trimester, progesterone produced by the corpus luteum is critical to the maintenance of early pregnancy until the placenta takes over this function at 7 to 9 weeks of gestation, hence its name (pro-gestational steroidal ketone). Indeed, removal of the source of progesterone (the corpus luteum) ***(Csapo and Pulkkinen, 1978)*** or administration of a progesterone receptor antagonist ***(***readily induces abortion before 7 weeks (49 days) of gestation ***(Peyron et al., 1993).***

The role of progesterone in later pregnancy, however, is less clear. Recent data suggest that progesterone may be important in maintaining uterine quiescence in the latter half of pregnancy by limiting the production of stimulatory prostaglandins and inhibiting the expression of contraction - associated protein genes (ion channels, oxytocin and prostaglandin receptors, and gap junctions) within the myometrium ***(Challis et al., 2000).***

## 2.AIM / OBJECTIVES

To evaluate serum progesterone as a method of predicting preterm labor in pregnant women from 24 to $36^{+6}$ weeks gestation by measuring serum progesterone level of pregnant women with preterm labor and comparing it to levels of pregnant women without preterm labor.

## 3.RESEARCH QUESTION

In pregnant women, can serum progesterone level be used as a method of predicting preterm labor?

## 4.RESEARCH HYPOTHESIS

In women with preterm labor, serum progesterone may predict the occurrence of labor accurately.

## 5.MEDICAL APPLICATION

Using serum progesterone level as a predictor of preterm labor and rationale of using progesterone supplementation to prevent preterm labor.

## 6.METHODOLOGY:

**Patients and Methods/ Subjects and Methods/ Material and Me**

- **Type of Study:** Nested case control study
- **Study Setting:** Ain Shams Maternity Hospital.

**Study Population:**

- 120 cases. All cases will have a serum progesterone level withdrawn and will be followed up. Cases who develop preterm labor will have their serum progesterone level, which was withdrawn at the beginning of the study, compared to the serum progesterone level withdrawn from a similar case with the same criteria but she did not develop preterm labor.

**Inclusion criteria:**

- Singleton pregnancy
- Gestational age (from 24 - 36+6 weeks).
- BMI: average 19 - 24.
- Ultrasound: in late first trimester (crown rump length between 9-11 weeks gestation), for accurate calculation of gestational age.

**Exclusion criteria:**

Patients with

- Anemia (hemoglobin < 10.5g/dl)
- Pre-existing chronic infective disease
- Multiple pregnancy
- Polyhydramnios
- Diabetes mellitus
- Preeclampsia – eclampsia
- Liver disease
- Renal disease
- Alcoholics
- Smokers
- Cerclage in cases of incompetent cervix
- Previous history of abortion or PTL due to incompetent cervix
- Intrauterine fetal death
- Rupture of membranes
- Congenital fetal malformation
- Not taking progesterone supplementation

**Sample size justification:**

MedCalc® version 12.3.0.0 program was used for calculations of sample size, statistical calculator based on 95% confidence interval and power of the study 80% with α error 5%**,** According to a previous study ***(Sanad et al., 2013),*** showed that the mean of progesterone between Preterm and At term (80.6±27.5 & 116.1±15.8) respectively and mean diff. (35.5) with p-value (<0.001), So it can be relied upon in this study, based on this assumption, sample size was calculated according to these values produced a minimal samples size of 57 cases were enough to find such a difference. Assuming a drop-out ratio of 5%, the sample size will be 60 women in each group.

**Methods:**

After approval of Ain Shams Maternity Hospital ethical committee, all women participating will be subjected to the following:

1. **Informed written consent will be obtained**
2. **History taking:**
   - Personal history.
   - Obstetric history: parity and history of abortions.
   - Menstrual history: history of sure and reliable menstrual period (LMP).
   - Late first trimester or early second trimester U/S to confirm gestational age.
   - History of cerclage
   - Past medical history
   - Past surgical history
3. **Examination:**
   - General examination: pulse, blood pressure, temperature, urine albumin, BMI.
   - Abdominal examination (fundal level, presence of scar of previous operations, uterine contraction)
   - Vaginal examination by sterile Cusco speculum examination (cervical dilatation, effacement, position, consistency, status of membranes, presentation and station)
   - Assessment of fetal wellbeing.
4. **Investigations:**
   - Serum progesterone level:

Five milliliters of blood will be collected by venipuncture and will be allowed to clot in tubes at room temperature. Serum will be separated within 2 hours and stored at -20°C until final estimation for serology. Immunoassay for the in vitro quantitative determination of progesterone in human serum and plasma by electrochemiluminescence immunoassay "ECLIA" is intended for use on **cobas**® e 411 immunoassay analyzers.

- **Statistical Analysis:**

The collected data will be tabulated and statistically analyzed using SPSS program (Statistical Package for Social Sciences) software version 20.0

Descriptive statistics will be done for numerical parametric data as mean±SD (standard deviation) and minimum & maximum of the range and for numerical non parametric data as median and $1^{st}$& $3^{rd}$ inter-quartile range, while they will be for categorical data as number and percentage.

Inferential analyses will be done for quantitative variables using independent t-test in cases of two independent groups with parametric data and Mann Whitney U in cases of two independent groups with non parametric data.

Inferential analyses will be done for qualitative data using Chi square test for independent groups. The level of significance taken at P value <0.050 is significant, otherwise is non significant. The p-value is a statistical measure for the probability that the results observed in a study could have occurred by chance.

**Ethical consideration**

The procedure set out in this study protocol, pertaining to the conduct, evaluation and documentation of this study, are designed to ensure that the investigators abide by the principles laid down in the current revision of the declaration of Helsinki.

## 4.REFERENCES


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