

**The Role of Prophylactic Vaginal Progesterone
in the Prevention of Spontaneous Preterm
Labour in Twin Pregnancy.
A Comparative Study**

Thesis

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LIST OF ABBREVIATIONS

| | |
|----------------|---|
| 17 OH P | 17-hydroxyprogesterone |
| ACOG | American college of obstetrics and gynecology |
| ART | Assisted Reproductive Technologies |
| ASRM | American Society for Reproductive Medicine |
| BMI | Body mass index |
| CI | Confidence interval |
| CL (Cx) | Cervical length |
| COX | Cyclooxygenase |
| DC | Dichorionic |
| DZ | Dizygotic |
| ECV | External cephalic version |
| EFW | Estimated fetal weight |
| GA | Gestational Age |
| hCG | Human chorionic gonadotropins |
| IM | Intramuscular |
| IVF | In Vitro Fertilization |
| MC | Monochorionic |
| MZ | Monozygotic |
| NICHD | National Institute of Child Health and Human |
| MFMU | Development Maternal-Fetal Medicine Units Network |
| NICU | Neonatal intensive care unit |
| NS | Non significant |
| OMP | Oral micronized Progesterone |
| OR | Odds ratio |
| P | Progesterone |
| PIH | Pregnancy induced hypertension |
| PG | Prostaglandins |
| PPRAG | Peroxisome proliferator activated receptor gene |
| PPROM | Preterm premature rupture of the membranes. |
| PTB | Preterm birth |
| SPB | Spontaneous preterm birth |
| TAS | Transabdominal sonography |
| TRAP | Twin reversed arterial perfusion |
| TTTS | Twin-twin transfusion syndrome |
| TVS | Transvaginal sonography |
| VBAC | Vaginal birth after cesarean delivery |

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ABSTRACT

Twin pregnancy is considered as a risk factor of preterm labor, which is responsible for the high rate of perinatal mortality and morbidity associated with this condition. The objective of this study was to evaluate the role of vaginal Progesterone in the prevention of SPB in twin pregnancy. One hundred women pregnant in twins were enrolled for this study. They were divided in 2 groups. Group (1) 50 pregnant women received vaginal progesterone 200mg daily for 10 wks (from the 24th to the 34th week of gestation). Group (2) 50 pregnant women received placebo for the same duration. Transvaginal ultrasound measurement of the cervical length was done at 18-24 weeks gestation.

This study showed that the prophylactic vaginal progesterone administration has no significant value in the prevention of SPB in twin pregnancy.

Keywords: Twin pregnancy, SPB, Vaginal progesterone.

INTRODUCTION AND AIM OF WORK

The numbers of multiple gestations have increased significantly in the past two decades. This change can be attributed to an increase in the use and success of assisted reproductive technologies.

Twin pregnancy is considered as a high risk condition.

Because perinatal morbidity and mortality are increased in multiple gestations, practitioners of obstetrics should familiarize themselves with these complications and their management and prevention.

The high rate of perinatal mortality and morbidity associated with twin pregnancy is mainly due to prematurity. The rates of preterm birth are increasing worldwide. Being born prematurely in an under-resourced setting puts a baby at extremely high risk of death in the neonatal period.

A method that may better identify women at high risk with either singleton or twin pregnancies is ultrasonographic measurement of cervical length at 20 to 24 weeks of gestation.

Several therapies have been introduced to prevent SPB in twin pregnancies without defined indications and with no evidence about under which circumstances these interventions would have any benefit.

The aim of this work is to find if the prophylactic administration of vaginal progesterone will show a reduction in the frequency of preterm birth among women with twin pregnancy.

CHAPTER 1

Epidemiology and Biology of Multiple Pregnancy

The definition of twinning has changed radically with the implementation of infertility treatment over the past two decades. At the present time, simple definitions of twinning are unsuitable to encompass the whole spectrum of multiple gestations as seen by modern, technologically astute clinicians. In order to formulate the most appropriate definition of twinning, it is necessary to consider the following:

(1) The *definition should include multiple gestations that do not end with more than one fetus/neonate*. Thus, cases of singletons following embryonic or fetal demise, following spontaneous or iatrogenic reduction, should be considered as a multiple gestation. This definition should also include combinations of a fetus and a complete hydatidiform mole.

(2) A pregnancy should be defined as *intracorporeal* rather than intrauterine to include multiple gestations of the heterotopic type. These are encountered much more frequently following assisted reproduction. The definition should exclude twins produced by cloning, but may include monozygotic (MZ) twins in whom zygotic splitting occurred *in vitro*.

(3) The *number of zygotes* at the beginning of gestation should be considered in the definition in order to include cases of conjoined twins, and inclusion of a set of MZ twins among a higher order multiple pregnancy.

(4) The *production time* of the zygote(s) should be incorporated in the definition to include cases of *superfecundation*, which may occur during ovulation induction and assisted reproductive technologies (ART). The

definition should enable consideration of two embryos produced in the same ovulatory cycle but transferred on different occasions as *biological twins* that develop as singletons in different pregnancies. As an exception to the definition, and due to the advent of cryopreservation, it may also include thawed embryos produced in different cycles but transferred simultaneously in one cycle.

(5) The definition disregards the source of zygote(s) in order to include multiple pregnancies resulting from transferred fertilized donor eggs, or multiples developing in a surrogate womb (***Blickstein and Keith, 2007***).

Bearing in mind these points, the following definition of multiple pregnancy is proposed. *Irrespective of the final number of fetuses/neonates, a multiple pregnancy is the result of intracorporeal development of more than one zygote and/or the intracorporeal development of a split zygote, which was produced in the same or in a different ovulatory cycle.*

Only the future will reveal whether the definition is sufficiently comprehensive for all types of spontaneous and iatrogenic multiple pregnancies (***Blickstein and Keith, 2001***).

Incidence

In human pregnancies, twins occur with an approximate frequency of 1 in 90 births (***Benirschke and Masliah, 2001***). This rate is known to vary widely from country to country with the highest numbers in Nigeria and the lowest in Japan (***Nylander, 1981***).

In general, the number of multiple births in a population can be estimated using Hellin's hypothesis (***Hellin, 1985***).

The race and age of the mothers carrying multiple gestations in the United States has also changed. Twinning used to be substantially more

common in black women, but since the 1980s, the levels of twinning in white women have risen at a higher rate and have eliminated the difference. Rates among Hispanic women have increased, but still remain lower than non-Hispanic black and non-Hispanic white mothers. In 1997, the twin births rates were 19.5 per 1000 births for Hispanic women, 30.0 for non-Hispanic black women and 28.8 per 1000 for non-Hispanic white women (*Martin and Park, 1999*).

Historically, age-specific twin birth rates rose steadily up to age 39 years, then dropped quickly. Since 1992, age-specific twin birth rates have been climbing. Women aged 45 to 49 years are three times more likely to have a twin gestation than at age 35 to 39 years; for women 50 to 54 years of age, one in every three births is a twin delivery (*Martin and Park, 1999*).

Over the last 25 years, an increase has occurred in the incidence of twin and high-order multiple gestations (i.e., triplets or more). This marked rise is due not only to the older age at childbearing but also to the use of fertility drugs to superovulate the ovaries (i.e. clomiphene citrate and gonadotropins), as well as the transfer of multiple embryos during ART procedures (*Rebar and DeCherney, 2004*). When compared with natural ovulation during which one egg is normally fertilized, IVF induces a 20-fold increased chance of twins and a 400-fold increased chance of triplets or quadruplets (*Brinsden, 2003*). In 1997, 12% of all twins were born as a result of ART, 38% of high-order gestations were due to ovulation induction, and 43% of high-order gestations were due to ART (*Centers for Disease Control and Prevention, 2000*). In 2001, of all live births that resulted from ART, 35.8% were multiple gestations and 3.8% involved triplets or more (Fig. 1-1).