Oral Tocolytic Drugs in Treatment of Preterm Labor

Thesis

Submitted for Partial Fulfillment of
The M. D. Degree
(Obstetrics and Gynecology)

By
Mostafa Mohamed Ibrahim Salama
(M.B.B. Ch.; M.Sc.)

Supervised by

Professor Dr. Mohamed B. Sammour
Prof. of Obstetrics &Gynecology
Ain-Shams University, Cairo

Professor Baha M. Sibai, M.D.
Prof. of Obstetrics&Gynecology
University of Tennessee, Memphis

Professor Dr. Alaa Eldin M.K. Eletriby
Prof. of Obstetrics & Gynecology
Ain-Shams University, Cairo

Dr. Sherif A. AKL
Asst.Prof. of Obstetrics& Gynecology
Ain-Shams University, Cairo

Faculty of Medicine
Ain-Shams University
Cairo, EGYPT
1998

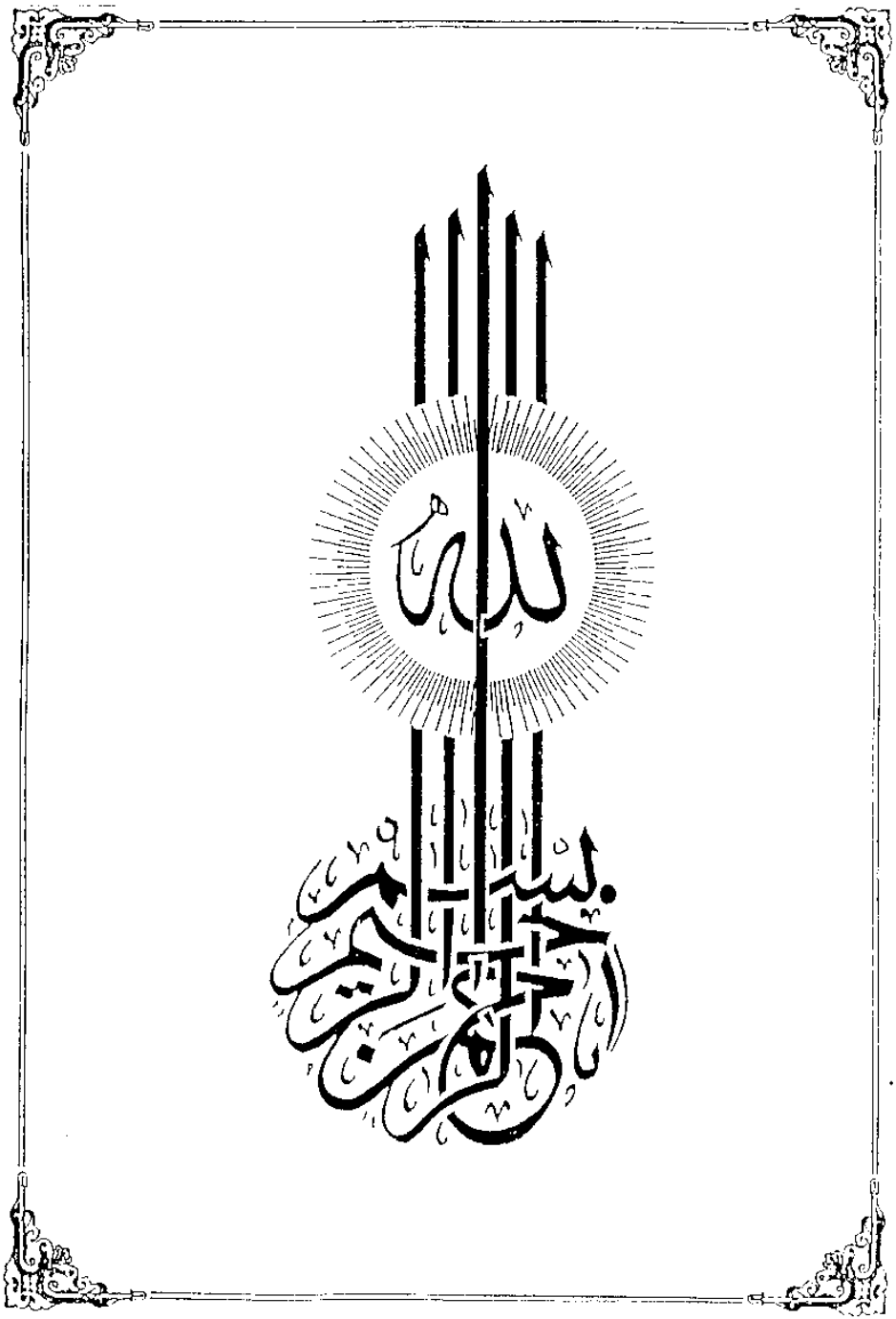

Table of Contents

Aim of the Work:

The primary objective of this clinical trial is to evaluate the efficacy of oral tocolytic agents in lowering the rate of preterm delivery, when given as maintenance therapy after successful inhibition of preterm labor.

As secondary objectives, this trial will investigate the effect of oral tocolysis upon:

1) Prolongation of pregnancy.
2) Recurrence of preterm labor.
3) Birth weight.
4) Neonatal morbidity.

Introduction:

Premature birth and low birth weight are the main issues in perinatal health care. Babies that are born too early or are born weighing too little are likely to die as infants, or if they survive, to be disabled. In 1979, 21 million low birth weight babies were born worldwide, which accounted for 17 percent of all births and 75 percent or more of the neonatal and infant deaths in that year (World Health Organization, 1980).

Today, powerful medications are capable of arresting the uterine contractility in early premature labor and of prolonging gestation for variable periods of time in a high proportion of cases. However, in no large population has it yet been demonstrated that the use of tocolytic drugs has reduced the rate of preterm births. In contrast, Boylan and O'Driscoll in 1983, documented a progressive decrease in prematurity and perinatal mortality without the use of tocolytic drugs.

Beta-adrenergic stimulants have been shown to depress preterm and term uterine contractions. As a result, various beta-adrenergic agents, such as ritodrine, salbutamol and terbutaline have been recommended for the inhibition of preterm labor. In the majority of trials, beta-adrenergic drugs have been initially administered parenterally for a variable period. Patients have then usually been placed on oral maintenance up to 36 to 38 weeks of gestation, although the need for continued treatment has not yet been demonstrated (Creasy et al. 1980).

Review of Literature

Preterm Labor and Delivery

Preterm labor and delivery have been a significant cause of perinatal morbidity and mortality for centuries. Although the introduction of refinements in neonatal care has improved outcome for small neonates, there has been no consistent documented decrease in the incidence of low-birth weight, preterm newborns for many decades. The problem of preterm birth has actually been magnified as the other causes of perinatal morbidity and mortality have decreased, so that preterm delivery is now the single most important problem to overcome in improving the outcome of the gestation with a nonanomalous fetus.

Definition:

Traditionally, all newborns weighing less than 2500 gm were classified as premature, but it is now known that as many as one-third of such neonates are born near term, but restricted in growth (Kaltreider and Johnson, 1976). A preterm birth is any delivery, regardless of birthweight, that occurs before 37 completed weeks from the first day of the last menstrual period (American Academy of Pediatrics, 1967 and World Health Organization, 1969). However, the lower limits of gestational age at which the phrase preterm labor and delivery can be used have never been well defined. Pregnancies ending before 20 completed weeks gestation are termed abortions; therefore, it seems reasonable to define preterm labor and delivery as occurring between 20 and 37 completed weeks (140 and 259 days) of gestation.

Incidence:

The true incidence of preterm delivery is not as well documented as might be expected, owing in part to lack of differentiation of growth-restricted from preterm infants. The British perinatal mortality survey, excluding 8 percent of births because of uncertain gestational age, found that 3.4 percent of births occurred before 251 days and another 6.1 percent between 252 and 265 days gestation (Butler and Bonham, 1963).

In the United States, data from a study of birth certificates for most of the country revealed the incidence of preterm birth to be 9.4 percent in 1981 which rose to 10.7 percent in 1989 (Monthly Vital Statistics, 1991). Significant racial differences exist with 8.8 percent of white births and 18.9 percent of black births having occurred preterm. A large multicenter trial in which gestational age was carefully assessed revealed an incidence of delivery before 36 weeks of 9.6 percent, adding credence to the birth certificate derived data (Cooper et al. 1993). Thus, the overall preterm birth rate is approximately 10 percent and will probably vary among different populations depending upon risk factors present.

Epidemiology of Preterm Labor:

I) Socioeconomic Status

Numerous reports show a strong correlation between preterm births and low socio-economic status, the latter being defined on the basis of educational level or of occupation and income (Frederick and Anderson, 1976; Papiernick and Kaminiski, 1974). Although black women are reported to have an incidence of preterm birth that is approximately double that of Caucasian women at all educational levels (Copper et al. 1996), black women who have more than 16 years of education have approximately two-thirds the preterm rate of those with less than 8 years of education (U.S. Department of Health and Human Services, Public Health Service, 1984).

Socioeconomic status also may have an impact on the nutritional status of a patient. The nutritional level at the time of conception affects the incidence of preterm delivery; the rate in women weighing less than 50 Kg at the start of pregnancy is three times the rate in women weighing 57 Kg or more (Frederick and Anderson, 1976). Several recent studies also demonstrate that inadequate weight gain during pregnancy is associated with an increased risk of preterm delivery of perhaps 50 to 60 percent (Abrams et al. 1989; Hediger et al. 1989).

Longitudinal studies of more than 30,000 births over 10 years show that there is a higher incidence of preterm delivery at both low and high maternal age (Bakketeig and Hoffman, 1981). The incidence is higher for women less than 20 years of age, not only for the first pregnancy, but also for the second or third. Mothers 35 years or older at first delivery are at the highest risk. However, maternal age exceeding 35 is not associated with an increased incidence of preterm birth unless childbearing begins after 35 years.

II) Medical History

The incidence of preterm labor and birth correlates with previous reproductive performance in all reports. A history of one previous preterm birth is associated with a risk of recurrent preterm labor that varies between 17 and 47 percent, the incidence rising with two or more previous preterm births (Keirse et al. 1978; Bakketeig and Hoffman, 1981; Roberts et al. 1990; Salama et al. 1994). With each birth that is not preterm, the risk of a subsequent preterm birth decreases. Although some reports suggest an increased incidence of subsequent preterm labor following one first abortion, properly controlled reports show no risk (Keirse et al. 1978; Linn et al. 1983). Most, but not all reports show an increased risk of preterm delivery after multiple first-trimester abortions (Papaevangelou et al. 1973). However, there appears to be little question that second-trimester abortions are associated with subsequent increased risk.

Incompetence of the cervix due to an inherent defect, which can lead to preterm delivery, is relatively rare. The rate of preterm birth following cerclage approximates 30 percent (Medical Research Council, 1988 and Rush et al. 1984). Cervical incompetence may occur because of dilation of the cervix beyond 8mm at induced abortion or cone-biopsy, but its incidence and its effect on preterm labor and delivery are poorly delineated. Preterm delivery rates ranging from 0 to 33 percent have been reported to follow cone-biopsy (Weber and Obel, 1979).

Approximately 3 to 16 percent of all preterm births have proved to be associated with uterine anomalies. The risk of preterm labor with a specific uterine anomaly is not known, however, because the incidence of uterine anomalies is not established. In one series of 265 pregnancies occurring in 126 patients with proven uterine anomalies, 29 percent ended in abortion. The incidence of preterm labor varies from 4 to 17 percent in patients with a septate uterus to between 18 and 80 percent in those with other proven anomalies (Heinonen et al. 1982). In addition, the T shaped uterus that may be present in women exposed in utero to diethylstilbestrol is often associated with preterm labor

and birth (Herbst et al. 1980). Preterm birth rates of approximately 15 to 30 percent have been reported in these patients. The incidence is greatest in those patients with associated demonstrated malformations of the genital tract. Multiple large leiomyomata may also increase the risk.

III) Habits During Pregnancy

A number of publications indicate that there is a relationship between strenuous and physically demanding employment and preterm labor (Mamelle et al. 1984; McDonald et al. 1988), whereas other reports show no deleterious effects (Berkowitz et al. 1983; Hartikainen-Sorri and Sorri, 1989). In one prospective study, preterm delivery was highest in women with standing occupations and lowest in those with active jobs, such as nurses, physicians, and athletes (Teitelman et al. 1990). The reported increased incidence of low-birth-weight newborns delivered of female physicians during residency training has been shown to be due to an increase in fetal growth retardation and not to preterm delivery in one report (Grunebaum et al. 1987), but others indicate that the spontaneous preterm birth rate is also increased (Schwartz RW, 1985; Miller et al. 1989).

Maternal smoking not only decreases birth weight, but also increases the incidence of preterm birth, the risk increasing with the number of cigarette s a day smoked (Meyer and Tonascia, 1977; Frederick and Anderson, 1976; Wen et al. 1990). Parous smokers may be at especially high risk (Cnattingius et al. 1993). It is not known whether the association between alcohol and low birthweight produces its effect on fetal growth or gestational age.

Illicit drug use in pregnancy is associated with preterm birth: Cocaine use in pregnancy has an attendant incidence of preterm birth of 20 to over 50 percent in matched studies (Chasnoff et al. 1989; Cherukuri et al. 1988).

The frequently reported anecdotal association of preterm labor and psychological trauma has received further support from studies demonstrating an association between adverse life events and preterm labor and delivery (Newton and Hunt, 1984; Lobel et al. 1992).

IV) Pregnancy Complications

Asymptomatic bacteriuria is associated with a higher rate of preterm labor if there is underlying renal disease or if acute pyelonephritis develops (Kincaid-smith P, 1968). Any systemic infection, such as bacterial pneumonia or acute appendicitis with sepsis, increases uterine activity, and endotoxins have been shown to stimulate myometrial activity in experimental studies. Chronic hypertension may necessitate preterm induction, but has not been clearly shown to cause spontaneous preterm birth, even though preeclampsia may lead to a slightly increased risk of preterm labor (Bakketeig and Hoffman, 1981). Diabetes is not a risk factor unless complications such as polyhydramnios develop. Women who have been treated for pituitary adenomas may be at higher risk (Magyar and Marshall, 1978), but treatment with bromocriptine dose not increase the risk (Singer et al. 1977). Patients with hyperthyroidism, heart disease, obstetric cholestasis, hepatitis, and anemia are also at increased risk, but the exact risk is not clear (Klebanoff et al. 1991). Abdominal surgery during the last two trimesters is usually associated with excessive uterine activity that may progress to preterm labor (Holbrook et al. 1989).

Assisted reproductive technologies (ART) are associated with a preterm birth incidence of approximately 27 percent (Australian Institute of Health and Welfare, 1992). In part this is due to an incidence of multiple pregnancies of approximately 20 percent, and the associated increased preterm delivery rate, but the incidence in singleton ART pregnancies is also quite high being approximately 15 percent.