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Tocolytic Effect of Magnesium Sulphate in Management of Preterm Labor

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بسم الله الرحمن الرحيم

(يَرْفَعِ اللَّهُ الَّذِينَ آمَنُوا مِنْكُمْ وَالَّذِينَ أُوتُوا الْعِلْمَ دَرَجَاتٍ وَاللَّهُ بِمَا تَعْمَلُونَ خَبِيرٌ)

(المجادلة: 11)

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الإهـــداء

إلى أبـي وأمي ...

الشمعتان اللتان أنارتا دربي وحياتي

إلى زوجي ...

نعم السانـد والداعم في بحثي ودراستي

إلى سجى وخالد ....

قرتـــا عيـنـــي

د. هديل قحطان الجميلي

2005

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I wish to express my deep thanks to all doctors who help and support me in this work .

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الملخص باللغة العربية

تعتبر الولادة المبكرة واحدة من أهم مشاكل الحمل والولادة ، حيث تشكل السبب الرئيسي لوفيات الأطفال الحديثي الولادة وتمثل نسبة 75% من وفياتهم و 35% من العناية الطبية لهم.

تعريف المخاض المبكر: هو التقلصات الرحمية المنتظمة التي تحدث قبل الأسبوع 37 من الحمل والتي تؤدي إلى اتساع عنق الرحم وينتج عنها ولادة طفل يزن أقل من 2500 غرام.

والأطفال الخدج يكونون معرضين لانواع عديدة من الأمراض المتعلقة بعدم نضوج أعضاء الأجهزة في أجسامهم والتي تؤدي الي مشاكل ومعوقات طويلة الأمد وبالرغم من الدراسات والبحوث التي أجريت خلال العقود الأربع الماضية فإن نسبة الأطفال الخدج لم تتغير ، بل على العكس هنالك بحوث تثبت زيادة هذه النسب ، بينما نسبة البقاء على قيد الحياة ازدادت وقلت نسبة الإصابة بالأمراض المتعلقة بهم وذلك بسبب التطور التكنولوجي في طب الأطفال الخدج والحديثي الولادة . هناك ما يقارب 5.5 مليون امرأة في العالم يعانين من مخاض مبكر.

هذه الدراسة المستقبلية أجريت لمعرفة تأثير عقار كبريتات المغنسيوم على آلام المخاض المبكر والتي أجريت في مستشفى الثورة العام النموذجي في صنعاء في فترة ستة أشهر ابتداء من الأول من كانون الثاني 2005م حتى نهاية حزيران 2005م حيث ان اجمالى عدد الولادات في هذة الفترة كان 5183 ولادة منها 239 ولادة مبكرة (4.6%).

اشتمل البحث على 100 حالة قسمت إلى مجموعتين وهي مجموعة البحث وعددها 50 حالة ومجموعة التحكم وعددها 50 حالة أيضاً.

أعطيت كبريتات المغنسيوم لمجموعة البحث لإيقاف تقلصات الرحم لمدة 48 ساعة لتمكين الجنين خلالها من الاستفادة من عقار الكورتزون والذي يحقن للأم عضلياً وذلك للمساعدة في نمو رئتي الجنين.

الجرعة: الجرعة البدائية بمزج مقدار 5 غم من كبريتات المغنسيوم ضمن 100 مل من محلول الدكستروز 5% وتعطى للمريضة خلال فترة 20 – 30 دقيقة.

جرعة الصيانة: 5 غم في محلول الدكستروز 5% (500 مل) بحيث تكون 1 – 2 غم بالساعة خلال الـ 24 ساعة القادمة.

مجموعة التحكم لم تعطَ أي عقار وتم رقودهن في المستشفى للإشراف والمتابعة فقط مع الراحة التامة وإعطاء المحاليل الوريدية والسوائل عن طريق الفم.

نتائج الدراسة:

1. 78% من الحوامل استجبن لعقار كبريتات المغنسيوم وكان إيقاف التقلصات الرحمية لأكثر من 48 ساعة حيث أعطيت الأم خلال هذه الفترة عقار الـــ كورتزون وهو الديكساميثازون 6 ملغم كل 12 ساعة (4 جرعات خلال 48 ساعة).
2. 22% من الحوامل لم يستجبن للعقار ولم يـــنجح فـــي إيقـــاف التقلـــصات الرحمية المبكرة وكانت الولادة في أقل من 48 ساعة.
3. نسبة الوفيات للمواليد الخدج ذوي الأوزان أقل من 1.5 كغم هي15%.
4. مجموعة التحكم 36% من الحوامل مستمر حملهن و 64% ولـــدن ولادات مبكرة.

* نستنتج من البحث أن لكبريتات المغنسيوم فائدة كبيرة في إخماد آلام الـــولادة المبكرة ويستعمل هذه العقار بشكل رئيسي في مستشفياتنا وذلـــك لقلـــة كلفتـــه المادية ولكونه يعطي أقل نتائج ثانوية وأعراض جانبية على الأم والطفل.

Abstract

Objective :

To evaluate the tocolytic effect of MgSo4 to stop uterine contraction in preterm labor .

Study Design :

This is a prospective case-control study done in obstetric unit at Al-Thawra Hospital on women with preterm labor of gestational age between 24-34 weeks through 6 months started from the 1st of January up to the 30th of June 2005.

Study Setting :

Obstetric unit at Al-Thawra Hospital in Sana'a city / Yemen .

Population :

100 women , 50 women(study group) had preterm labor and 50 women (control group) with preterm labor at gestational age between 24-34 weeks admitted to the obstetric unit in Al-Thawra general Hospital/Sana'a/Yemen .

Results :

There were(5183) deliveries at Al-Thawra General Hospital between the 1st of January to the 30th of June/2005, (239) women had preterm labor , with an incidence of (4.6%) , of them 50 women had received MgSo4 to stop uterine contraction and (50) women control cases .In (39) patients(78%)of the study group we succeeded in delaying delivery for more than 48hours by using MgSo4&during that period the mother received dexamethason 6mg every 12 hours for 4 doses . (11) patients (22%) delivered in less than 48 hours .In control group (18) patients (36%) had false labor pain and they were discharged home with good general condition while (32) patients (64%) delivered on less than 48 hours(in this group only bed rest , hydration and sedation was given) .

Conclusion :

Preterm labor is one of the most common cause of increased perinatal morbidity and mortality . In this study we found that the use of MgSo4 as a tocolytic is effective in stopping uterine contraction .

Introduction

Preterm delivery with its associated morbidity and mortality still represents one of the major unsolved problems in obstetrics in 7-12 % of pregnancies, and depending on population , results in up to 75% of neonatal morbidity and mortality (Jorge D. Blanco et al & V.Daniel et al ,2000).It accounts for 35% of all health care spending on infants (Am J obstet. Gynecol 2003). 20% of preterm deliveries are caused by obstetric intervention for maternal or fetal indications, 80% are spontaneous. In fact the incidence of preterm deliveries has increased from 9% to 11% since 1970 (Tucker JM et.al. 1991).

That the preterm infants are at risk for specific diseases related to immaturity of various organ system , also associated with long-term morbidity that leads to neuro development handicaps (Steven G. et al).

During 20 to 30 years , there has been a significant improvement in the survival rate of small neonates , and accompanying improvement in the rate &outcome from some of these morbid occurances.Neonatal mortality has decreased from 7 per 1000 live birth in 1985 to 4.9 per 1000 live birth in 1995. This decrease has been predominantly caused by significant improvements in neonatal care (Clinical obst.& Gynecol. Vol. 43/2000). The late fetal death rate (stillbirth rate) has also decreased from 4.9 per 1000 live births in 1985 to 3.6 per 1000 live birth .

The combined decrease in neonatal and stillbirth rate has resulted in an overall decrease in the perinatal mortality rate from 10.7 to 7.5 per 1000 live birth .There is no reduction in the national rate of preterm deliveries . Because of lack of understanding the cause and pathophysiology of preterm labor , and because of confusion about the definition of preterm labor, it is difficult to determine the difference between those women with uterine contraction without subsequent consequence and those who will proceed to early delivery .As the last menstrual period is unknown in 20% of pregnant

women , therefore fetal sonar biometry is an accurate way of assessing the predicted date of confinement (Kramer et al 1988).

NO treatment has been shown to reduce the rate of premature delivery with clinical significance (Guyetvai K, et al 1999). However there is evidence that some tocolytic agents delay delivery for days at time usually long enough to allow for steroid administration and maternal transfer to a tertiary care center .

- The incidence of handicap remains at 6-7% of all preterm birth .
- Despite 4 decades of research, the rate of premature births has not changed , and some data indicate the rate may be worsening .
- Survival rates have increased and morbidity has decreased because of technologic advances in perinatal and neonatal medicine.
- The etiology of preterm labor is poorly understood but there are multifactorial problems and certain associated factors that lead to increase morbidity and mortality.
- Neonatal morbidity in USA decrease from 7/1000 to 4/1000 in 1985.
- The estimated number of preterm birth world wide is nearly 13.000 (villar & Ezcurra 1994)
- About 5.5 Million women world wide are at potential state of preterm labor .

Aim of study

The ultimate goal in this study is to delay preterm delivery for 48 hours by using tocolytic(Mgso4)to stop uterine contraction to allow time to give dexamethason to improve lung maturity in order to deliver an infant without of the sequelae of prematurity and it is achieved by stop myometrial contractions by tocolytics, that their action do not prevent preterm birth, but can delay delivery for at least 48 hours an important interval during which effective antenatal intervention to reduce neonatal morbidity and mortality may be accomplished and maternal transfer to a tertiary care center . .

Our study concentrates on Magnesium Sulphate infusion which used in our hospital for suppression of premature uterine contraction.

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Definition

Preterm labor: labor occurring before 37 weeks of gestation (259 days from the first day of the last menstrual period, that associated with regular painful ,frequent uterine contractions causing progressive effacement (greater than 80%) and dilation of the cervix (>2cm) (21)

Incidence of preterm labor 5-15% of all pregnancies rates have remained unchanged for decades despite effort to intervene.

* Preterm labor divided into :
- Early preterm labor < 32 weeks.
- Late preterm labor > 32 weeks.
- Indicated or spontaneous preterm labor (21).

* Biochemical markers for less than 32 weeks of gestation
- α -fetoprotein .
- Alkaline phosphatase.
- granulocyte colony stimulating factors(66).

* Biochemical markers for more than 32 weeks of gestation increase level of estriol in saliva.
- Induced preterm labor accounts 20-30% .
- Spontaneous preterm labor accounts 70-80% (3).

* Complications in very premature infants include :
  - Respiratory distress syndrome (RDS).
  - Intraventricular hemorrhage (IVH) .
  - Broncho- pulmonary dysplasia (BPD).

- Patent ductus arteriosus (PDA) .
- Necrotizing enterocolitis (NEC) .
- Sepsis .
- Apnea .
- Retinopathy of prematurity (ROP) (1).

Long – Term Morbidity :

Preterm infants are at increase risk for neuro-development handicaps(2) such as:

- Sever mental retardation (IQ<70) .
- Cerebral palsy .
- Seizure disorders .
- Blindness .
- Deafness .

Risk factors for preterm labor:

*** General causes:**

- Previous preterm delivery.
- Low socio economic status .
- Non-white race.
- Maternal age < 18 years > 40 years.
- Preterm premature rupture of membrane PPROM .
- Multiple gestation .
- Maternal history of one or more spontaneous second- trimester abortion .

*** Fetal causes:**

- Intrauterine fetal death .
- Intrauterine growth retardation .

*** Abnormal placentation .**

*** Presence of retained intrauterine contraceptive device.**

*** Maternal complications (Medical or obstetrics) .**

- Maternal behaviors.
- Smoking .
- Alcohol abuse.
- Lack of prenatal care.

*** Infections causes:**

- Chorioamnionitis..
- Bacterial vaginosis .
- Asymptomatic bacteruria .
- Acute pyelonephritis.
- Cervical / vaginal colonization .

*** Uterine causes:**

- Myomata (particularly submucosal or sub placental) .
- Uterine septum.
- Bicornuate uterus.
- Cervical incompetence.
- Exposure to diethyl stillbestrol (DES).

The Epidemiology and pathogenesis of spontaneous preterm labor :

Early preterm birth is more likely to recur & it is more strongly associated with a short cervix and the presence of fetal fibronectin in cervicovaginal secretions and is more often accompanied by clinical or subclinical evidence of infection and by long-term morbidity for the infant . Later preterm birth is more likely to be associated with increased uterine contraction frequency and with rise in maternal excretion of estriol (an indicator of increasing maturation of the fetal hypothalamic pituitary – adrenal axis) , and thus to mimic normal labor at term(21).

Non recurrent preterm birth :

Risk factors for non recurrent spontaneous preterm birth include: second trimester bleeding ,abnormal amniotic fluid volume , multiple gestation , substance abuse and trauma. These events have in common that they may lead to ischemia, injury or disruption to the junction of the maternal decidua with the fetal chorion .

Recurrent preterm birth :

It is associated with prior preterm birth , especially before 32 weeks . It is associated with the following risk factors(39) :

1. Obstetric history and preterm birth :

The risk of spontaneous preterm birth is increased by history of prior preterm delivery.

The recurrence risk rises as the number of prior preterm births increase.

The likelihood of recurrent preterm birth also increases as the gestational age of the prior preterm birth decreases(5,7).

2. Maternal race and preterm birth :

African – American women have a rate of preterm delivery that is approximately twice that of women of other races.

The ratio of black to white preterm birth rates in 1995 was (1.95). (3 ,37)

The incidence was 5.7% in white Europeans but 9.4 – 10.2% in Africans (Steer et al . 1995).

3. Infection and Prematurity :

The association between preterm birth and infection has been reported for more than 50 years(Knox JC, et al 1950).

Infection comes from multiple sources:

-Epidemiologic, Microbiologic, histological and clinical .

-Maternal and neonatal infections occur more frequently after preterm-than term birth .

-Numerous microorganisms have been recovered from the lower and upper genital tract and amniotic fluid of women with preterm labor and preterm ruptured membranes (Wahbeh CJ et al.1994).

-Another study found that both positive membrane cultures and increased amniotic fluid IL-6 levels occur more frequently in spontaneous than indicated preterm births.(47)

-Infection out side the genital tract have also been related to preterm birth , most commonly urinary tract and intra abdominal infections (e.g. pyelonephritis and appendicitis).(48)

-Bacterial vaginosis lead to alteration in maternal vaginal flora in which gram negative anaerobic bacteria and mycoplasma species largely replace the normally predominant lactobacilli .

-There is an association between Bacterial vaginosis and elevated level of endotoxin, IL - Iα, mucinase, and Sialidase , and suggested that bacterial vaginosis may result in the production of cytokines with biologic effects on the uterus, cervix and membranes.

4. Cervical length:

the length of the uterine cervix as measured by transvaginal ultrasonography is inversely and continuously related to the risk of preterm birth in both singleton and multiple gestation (67).

The shorter the cervical length at 18-28 weeks gestation, the greater are the risk of spontaneous prematurity(49,50,51).

Cervical length is also strongly related to a history of spontaneous preterm birth, especially before 32 weeks gestation(the earlier the gestational age at delivery the shorter the cervix in the next pregnancy) (4).

- The correlation between cervical length and preterm birth risk may be explained by the physical strength or resistance of the cervix to factors such as intrauterine weight or volume, biochemical influences arising from infections or other inflammatory stimuli, or biophysical effects of uterine activity(Iams JD et al.1998).
- That cervical length is related to gestational age at delivery in both previous and future pregnancies indicates that cervical length is an independent risk factor for prematurity(13).

5. Fibronectin:

fibronectin is an extracellular matrix protein that is best described as the (glue) that attaches the fetal membranes to the underlying uterine decidua. It is normally found in the cervicovaginal secretions before 20-22 weeks of pregnancy , and again at the end of normal pregnancy as labor approaches. It is not normally present in cervicovaginal secretions between 22 and 37 weeks.

The presence of fibronectin in cervicovaginal secretions after 22 weeks is a marker of disruption of the decidual - Chorionic interface .Fibronectin status at 22-24 weeks was strongly correlated with the presence of bacterial vaginosis with subsequent histological chorio - amnionitis, postpartum endometritis and neonatal sepsis(66,52).

Screening tests

1. **Oncofetal fibronectin :**

This is an extra cellular protein concentration in the amniotic fluid and extra villous trophodecidual interface. It is found in the cervicovaginal secretions during the first 20 weeks of pregnancy and there after it disappears. On spontaneous rupture of membranes at term , it reappears again (*Lock wood et al 1991*) . It has high sensitivity for detection of subclinical rupture of membranes and preterm birth , but has low specificity and high rate of false positive results .(58) When it is detected at a level > 50 ng/ml it may be a sensitive and a specific mean to identify those women at subsequent risk of preterm labor and delivery (*Eriksen et al 1992*).

2.Screening for abnormal genital tract colonization :

Women who are colonized by Trichomonus vaginalis , Bacteriod species , Ureaplasma urealyticum have increased risk of preterm birth , preterm delivery and PPROM (*Minkoff et al 1984*).

Bacterial vaginosis is characterised by reduction in lactobacilli with increase of up to 1000 anaerobes and Mycoplasma hominis (Lamont 1995).Women with bacterial vaginosis between 8 and 17 weeks gestation had 2 to 6 folds increased risk of preterm birth (61). Bacterial vaginosis was associated with preterm delivery and low birth weight infants independent of other recognized risk factors . (60)

Rosenstein et al (1996) found that there was 3.3 fold-increased risk of preterm birth weight and 3.8 fold increased risk of pre labor rupture of the membranes in association with bacterial vaginosis .

Extracellular mucolytic enzymes (Mucinases & Sialidases) allow bacteria to penetrate the cervical mucus plug, and is found in higher concentrations in women with bacterial vaginosis (Mcgregor et al 1994).

3. Cervical scores :

More recently , reports of cervical scores in multiple pregnancies had been encouraging . Cervical score is based on both length and dilatation of the cervix & is expressed as cervical length in cm minus cervical dilatation in cm (*Newman et al 1991*) .

Transvaginal ultrasonography to measure objectively the length of the cervix more accurately is better than manual examination (*Anderson et al 1990*) It is also useful in selecting candidates for cerclage (*Craigo 1996*) .

4. Other screening test :

Several biochemical markers in maternal blood as predictors of preterm birth include serum collagenase , plasma corticotrophin releasing hormones, serum tissue inhibitor of metalloproteinase and serum relaxin. Maternal serum alpha fetoprotein is elevated in association with preterm labor and preterm pre labor rupture of the members (*Warren et al 1992*).

Increase in salivary estriol to progesterone ratio is a possible predictor of preterm labor (Darane et al 1987). It increases 3 weeks before the onset of term or preterm labor (Mcgregor et al 1995).

Urinary albumin measured in the early second trimester acts as a marker for predicting preterm delivery (*Perry et al 1993*).

Early diagnosis

Fetal breathing movements :-

These normally stop during labor. When women are admitted in preterm labor with apparent fetal breathing movements they generally do not progress for preterm labor and delivery (Castle & Turnbull 1983). In all cases absence of both fetal movements and fetal breathing movement was predictive of either intra-amniotic or neonatal infection (*Vintzileos et al 1985*).

Home uterine contractions

Early studies on home uterine monitoring depended on the patient education and self-feeling. They are means of early detection of preterm labor (*Hill et al 1990*).

Prevention of preterm labor :

- Education about preterm labor remains integral to prevention.
- weekly cervical examination have no demonstrated beneficial effect.
- In fact numerous cervical examinations may cause harm by introducing pathogens which may increase the risk of ascending infections.
- The benefits of home uterine monitoring and daily nurse contact are subjects of controversy except in case of multiple gestation.
- Prophylactic oral tocolytic therapy also has no demonstrated beneficial effect overall .
- Because of their side effects tocolytics agents should be avoided before the onset of true preterm labor.
- Decreased activity or bed rest in the late second trimester and early third trimester commonly is recommended, although no studies demonstrating the

efficacy of these measure have been done. Andrews et al (1991) found an advantage of routine hospitalization preventing preterm birth. (36).

- Cervical cerclage is recommended only for women who have been diagnosed with cervical incompetence and is not an appropriate treatment for cervical dilation due to preterm labor.
- Home uterine activity monitoring (HUAM) . This advocated for women with major risk factors for preterm births . These risk factors include multiple gestation . Its value is not yet established (Gardner and Goldenberg 97).

Diagnosis:

The only proof that labor is established is progressive dilation of the cervix with regular uterine contractions begins before the 37 weeks of pregnancy . However , once this has happened , it may be too late to attempt any preventive treatment (31) ,for this reason the diagnosis often has to be made on the basis of reported uterine contractions .

Braxton Hicks contractions occur in all pregnancies from about 24 weeks gestation onwards , and many women find them painful. This means that the diagnosis of preterm labor is often erroneous. Equally , women in real preterm labor are often misdiagnosed . The possibility of labor should always be considered in any pregnant women presenting with abdominal pain all too often the erroneous diagnosis of UTI is applied . (Mac Dermott 1994)

Investigations :

1. History of :

- Previous preterm labor.
- Previous preterm delivery or both.(33)
- Infection during present pregnancy or symptoms of current infection like upper respiratory tract infection or urinary tract infection.
- Recent intercourse.
- Physical abuse or recent abdominal trauma.
- recent drug abuse.

2. Examination

I. Sterile speculum examination :

- To rule out any evidence of rupture membrane, do nitrazine and fern test .
- Cervical culture including :

* Chlamydia trachomatis .

* Neisseria gonorrhea.

*Group B. hemolytic streptococci.

*Wet preparation for organisms causing bacterial vaginosistrichomonas.(33)

II.Bimanual examination: performed if there is no evidence of membrane rupture.

- The examination should be repeated at appropriate intervals to determine whether cervical changes has occurred.
- If rupture has taken place treatment of PROM should be initiated.

III.Laboratory studies.

- Blood sample for complete blood cell counts.
- Cervical specimens for culture.
- Urine specimens for toxicology screen .
- Urinalysis.
- Microscopic evaluation and culture.

- Sensitivity studies.

* Amniocentesis may be done especially if the patient does not respond well to tocolytic agents or if the patient is febrile without an obvious source of infection .

- If amniocentesis performed → Grams' stain .
  → Cell count .
  → Glucose culture.
  → Fetal lung maturity studies if gestational age between 30 – 35 weeks.

- The presence of fetal fibronectin in the cervicovaginal secretions is a marker for decidual disruption. Which is thought to be a potential diagnostic indicator.(33)

IV.Ultrasonography: to assess

- Fetal position .
- Calculate amniotic fluid index .
- Estimate fetal weight .
- Determine placental location .
- Detect evidence of abruption placenta .
- Identify fetal or uterine anomalies.
- Determine biophysical profile if indicated .

V.Continuous fetal heart monitoring :

Should be performed by cardiotocogram until patient is stable and the rate of contractions is less than 6 per hour for an extended period.(33)

Management:

1. **Intravenous hydration:** (a common initial management) This based on physiologic evidence that hypovolemia may be associated with increased uterine activity (Freda MC et al.1996).

Bolus of 500 ml of normal saline or Ringer's lactated solution can be administered.

This rapid intravascular expansion can diminish the contractions of an irritable uterus. The rate of intravenous fluid can then be adjusted to 100ml/ hour to avoid pulmonary edema during tocolytic therapy.

2. Antibiotics:

prophylaxis antibiotics against GBS infection should be initiated while the patient is in active preterm labor as a preterm neonate is highly susceptible to neonatal sepsis from these organisms.I.V Ampicillin 2gm 6 hourly with Erythromycin 250 mg 6 hourly for 48 hours. Followed by oral Amoxicillin 250 mg 8 hourly with Erythromycin 333 mg 8 hourly (for 5 days) .

Other regimen:

I.V. Ampicillin 2 gm 6 hourly for 24 hours followed by 500mg given orally 6 hourly until hospital discharged or delivery.(23,35)

3. Corticosteroids:

Antenatal steroids influence the synthesis of fetal proteins and peptides. In general glucocorticoids act to enhance cell differentiation and maturation rather than cell growth. Corticosteroids accelerate the appearance of pulmonary surfactant from type II pneumocytes and decrease the incidence of neonatal deaths, intracerebral hemorrhage and necrotizing enterocolitis.

* Two glucocorticoid regimens have been found effective:

- Betamethason: 12 mg intramuscularly every 24 hour for 2 doses.
- Dexamethason: 6 mg also given intramuscularly every 12 hours for 4 doses in 48 hours.

*The oral preparation of dexamethazon should not be used.

Other steroid preparations (e.g. prednisolone) are not effective because of poor placental transfer and should not be used.(55)

Corticosteroid should be administered to induce lung maturity in fetuses between 24-34 weeks of gestation, if no obvious sign of infection are present . (Gardener & Goldenberg)

Optimal benefit is achieved 24 hours after the second dose.

Corticosteroid therapy increase risk of infection for both baby and mother as well as impaired maternal glucose tolerance also lead to suppression of maternal or neonatal adrenal function and alteration of fetal biophysical profile (53,54) .

Corticosteroids decrease the incidence of intraventricular hemorrhage by 50% in preterm neonates.(32)

4.Tocolytic drugs :

Tocolytic drugs are the cornerstone of primary pharmacologic management of preterm labor . They are intended to stop uterine contractions during a current episode of preterm labor or maintain uterine quiescence after an acute episode (Am J obstet. Gynecol 2003).

It is usually indicated when regular uterine contractions are present with cervical change documented.

Cervical dilation of at least 3cm is associated with decreased success rate for tocolytic therapy .(34)

It is reasonable to begin treatment with tocolytic agents until 34 weeks of gestation .

Analysis of data from neonatal centers reveals that the survival rate of infants delivered at 34 weeks of gestation is within 1% of the survival rate of those delivered at 37 weeks of gestation .(33)

Numerous medications have been employed in an attempt to achieve tocolysis including B-mimetic, calcium channel blockers, magnesium, non - steroidal anti inflammatory drugs .

Non of these agents except Indomethacin have been shown to be efficacious in delaying preterm birth in singleton pregnancies for more than 48 hours. Comparatively speaking indomethacin had shown (in randomized trails) to prevent preterm labor with singleton pregnancies up to 7 days.(15)

Initial evaluation of preterm labor:

The initial evaluation of patient in preterm labor is focused on the risks and benefits of continuing the pregnancy for both mother and fetus . Potential causes of preterm labor should be sought in the initial evaluation and reassessed during the course of treatment.

Myometrial contractility and Tocolytic Action :

The key process in actin – myosin interaction and thus contraction is myosin – light – chain phosphorylation. This reaction is controlled by myosin light – chain kinase (MLCK) . The activity of tocolytic agents can be explained by their effect on the factors regulating the activity of this enzyme , notably calcium and cyclic adenosine monophosphate (cAMP).Calcium is essential for the activation of MLCK and binds to the kinase as calmodulin – calcium complex.

Depolarization leads to calcium influx through specific calcium channel blockers. Calcium can also enter through voltage-independent mechanism. Magnesium ions may interact here and also may compete with calcium for the voltage-dependent channels. Calcium is stored within cells in the sacro-plasmic reticulum and in mitochondria . Progesterone and (cAMP) promote calcium storage at these sites , while PGF 2alpha and oxytocin stimulate its release . Levels of (cAMP) are increased by the action of adenylate cyclase , which in turn is stimulated by β-adrenergic agents.

Goals of Tocolytics :

The goals are to prolong pregnancy while an effective regimen of corticosteroids can be administered to enhance fetal lung development.

Primarily tocoloysis should decrease uterine contractions and arrest cervical dilation when the lowest effective dose is used.

The drug should be decreased or stopped if significant side effect developed.

If intravenous or subcutaneous therapy has been used and has produced sustained clinical improvement for 12-24 hours, the agent should be discontinued. Although many practitioners advocate the use of oral tocolytics immediately after parenteral tocolytics, this practice has not been shown to prolong pregnancy.

Tocolytics used in the treatment of patients with preterm labor

Class of tocolytic	Types	Known or potential mechanisms of action
B-Mimetics	Fenoterol,hexoprenaline, isoxuprine,nylidrin, ritodrine, salbutamol, terbutaline	Binds to B1 and B2 receptors, increasing intracellular levels of cAMP, increases in cAMP initiate reduction in intracellular calcium, in turn inhibiting muscle contraction .
Calcium channel blockers	Nicardipine, nifedipine	Prevents entry of calcium in smooth muscle cells by blocking calcium channels and suppressing release of intracellular calcium stores.
Magnesium	Magnesiumoxide, magnesiumchloride, magnesiumgluconate, magnesium sulfate	At high levels displaces calcium from sarcoplasmic reticulum, thereby increasing repolarization time between contractions and decreasing force of contractions
NSAIDS	Indomethacin	Inhibits production of prostaglandins
Ethanol	Ethanol	Diminishes secretion of two neurohypopheseal hormones antidiuretic hormone and oxytocin

Contra indication to tocolysis :

Maternal contraindication:

- Significant hypertension(eclampsia, sever preeclampsia,chronic hypertention).
- Antepartum hemorrhage.
- Cardiac disease.
- Any medical or obstetric condition that contraindicates prolongation of pregnancy .
- Hypersensitivity to a specific tocolytic agent.

Fetal contraindication :

1. Gestational age > 37 weeks.
2. Advanced dilatation and effacement.
3. Demise or lethal anomaly .
4. Chorioamnionitis.
5. In utero fetal compromise.
   - Acute → fetal distress.
   - Chronic → IUGR or substance abuse.

1. Beta mimetics :

Mechanism of action

Two types of B- adrenergic receptors have been described B^1 receptors are prevalent in the heart , small intestine and adipose tissue . B^2 receptors predominate in the smooth muscles of blood vessels, uterus , bronchioles, and diaphragm. Stimulation of B_2 receptors also causes hepatic glycogen production and insulin secretion from pancreatic islet cells . B^2 agonists act on receptors in the uterus to increase cyclic adenosine monophosphate in smooth muscle cells which decrease free calcium and phosphorylates myosin light chain kinase thus inhibiting muscle contraction . They show a reduced effect after prolonged administration , and it is believed that a decrease in number of B-receptor is responsible for this reduced effect (41).

Efficacy :

There is evidence that the B-mimetic agents are successful in prolonging pregnancy for at least 48 hours and perhaps longer. (FDA) approved ritodrine as a parentral tocolytic in 1980 , but it is used less often than terbutaline because of perceived higher rate of maternal side effects(27).

Side effects and complications of B-mimetic tocolysis

Physiologic	**Fetal**
Apprehension	Tachycardia
Jitteriness	Cardiac arrhythmia
Headache	Myocardial & septal hypertrophy
Nausea & vomiting	Myocardial ischemia
Fever	Heart failure
Hallucinations	Hyperglycemia
Metabolic	Hyperinsulinemia
Hyperinsulinemia	Death
Hyperglycemia	**Neonatal**
Hyperlactacidemia	Tachycardia
Hypokalemia	Hypoglycemia
Hypocalcaemia	Hypocalcaemia
Antidiuresis , water retention	Hyperbilirubinemia
Altered thyroid function	Tachycardia
Elevated transaminases	Myocardial ischemia
Cardiac	Hypotension
Tachycardia	Intraventricular Hemorrhage
Pulmonary	Decreased Myocardial Contractility
Hypotension	
Arrhythmias/palpitations	
Heart failure	
Myocardial ischemia, altered ECG & chest pain	
Shortness of breath	
Other	
Skin rash	
Pruritis	
Ileus	
Death (cardiac)	

Date item Hill WC. Risks and complications of tocolysis Clin Obstet Gynecol 38:725 . 1995.

Contraindications and Relative Contraindications to B-Mimetic Tocolytics :

-Contraindications to *B*-Mimetic Tocolytics

- Maternal cardiac disease (structural, ischemia, or dysrhythmia).
- Eclampsia, sever pre-eclampsia,or other significant hypertensive disease .
- Significant antepartum hemorrhage .
- Uncontrolled diabetes mellitus .
- Maternal hyperthyroidism

-Relative Contraindications to *B*-Mimetic Tocolytics :

- Diabetes, both diet and insulin controlled .
- Hypertension .
- History of sever migraine headaches .
- Fever .
- Increased risk of pulmonary edema .

BOX 1

1. Use of Terbutaline in the Treatment of Peterm Labor :

Preparation of solution

Dissolve 5 ampoules of terbutaline (5 mg) in 500 ml of Ringer's lactate solution . This preparation contains 10µg of terbutaline per milliter.

Continuous intravenous infusion

Using a Harvard pump, start IV infusion at a rate of 5 µg/min (0.5 m1/min. 30 m1/hr) increase every 10 minutes by 5 µg/min (0.17 m1/min⁵ 10.2 m1/hr)until a rate of 15 µg/min (1.5 ml/min⁵ 90 m1/hr) is reached . If contractions have not disappeared with this dose a double-strength solution (5 mg in 250 ml of Ringer's lactate solution) should be prepared to avoid excessive intravenous fluid administration . Further increases should continue until contractions disappear , toxicity appears, maternal pulse rate exceeds 120 b.p.m , or a dose of 30 µg/min is reached . Once an adequate dose is reached , it should be maintained for 12 hours after the contractions stop . Do not taper down before switching to oral or subcutaneous treatment.

Subcutaneous treatment

Discontinue the infusion of terbutaline I.V and 15 minutes later give 250 µg subcutaneously.

Continue giving the same amount every 3 to 4 hours as necessary to keep the pulse rate between 100 and 120 bpm.

Oral treatment

Give a 5 mg tablet of terbutaline, and 30 minutes later discontinue the intravenous or subcutaneous administration . Give the same dosage every 4 hours for the first 24 hours as long as the pulse rate does not exceed 120bpm. Then adjust the dosage to 2.5 to 5.0 mg every 3 to 6 hours depending on the patient's response to therapy .

BOX 2

2. use of Ritodrine in the Treatment of Preterm Labor

Preparation of solution:

Dissolve 3 ampoules of ritodrine (150 mg) in 500 ml of D^5 W Ringer's lactate solution . The preparation contains 300 µg ritodrine / milliliter.

Continuous intravenous infusion :

Using a Harvard pump, start intravenous infusion at a rate of 100 µg/min (0.33 ml/min‡20ml/hr). Increase every 10 minutes by-50 µg/min (0.17 ml/min‡ 10.2 ml/hr)until the contractions stop , the pulse rate exceeds 120 bpm, toxicity appears, or a maximal rate of 350 µg/min (1.17 ml/min‡ 102 m1/hr) is reached . Once an adequate dose is reached , it should be maintained for 12 hours after the contractions stop. Do not taper down before switching to the oral treatment .

Oral treatment :

Give one tablet of ritodrine (10 mg) , and 30 minutes later discontinue the intravenous infusion . Continue the administration of one tablet every 2 hours for the first 24 hours after intravenous treatment as long as the pulse rate dose not exceed 120 bpm. Then adjust the dosage , and use 10 to 20 mg every 4 to 6 hours as necessary .

Dosage: →

Ritodrine is rapid acting serum levels reach 75% of maximum in 20,minutes .

Terbutaline is an off-label-used beta mimetic and can be administered in I.V , oral , and subcutaneous forms. Intravenous route is seldom used because of increase risk of pulmonary edema (42).

2. Calcium channel blockers :

Mechanism of action :-

Calcium antagonists inhibit the influx of calcium ions through the muscle cell membrane and reduce uterine vascular resistance .

The decreased intracellular calcium also results in decreased myometrial activity .

Efficacy: →

Nifedipine was reported in a small observational study to be effective in suppressing contractions and well tolerated by mother and fetus (43) .

In comparison with magnesium nifedipine was equally effective in delaying delivery for 72 hours.

Dosage: →

10 – 20 mg orally as initial dose , then 20mg orally every 6hours for 24 hours , then 20mg orally every 8 hours (do not use sublingual route) because of reports of profound hypotension and myocardial ischemia (44-46) .

Side Effects:

Maternal side effects : →

When compared with ritodrine , maternal side effects are less frequent and sever. The most common side effects are :

- Flushing .
- Headache .
- Dizziness .
- Nausea (Garcia – Velasco JA et al)

- Transient hypotension .
- Increase pulse rate .

Neonatal Side Effects : →

Calcium channel blockers can cross the placenta .

Ray et al (45) found no significant differences in Apgar scores or umbilical venous blood gas values .

3. Prostaglandin synthetase inhibitors :

Mechanism of action :

Prostaglandin synthetase inhibitors inhibit cyclo-oxygenase that decreases prostaglandin synthetase and block conversion of free arachidonic acid to prostaglandin .

Indomethacin is the most commonly used agent in this class .

Efficacy →

Indomethacin was first reported to delay delivery by more than 7 day in 80% of treated subjects (15) (in a randomized trials)

(Hig by et al 1993 and Gardener & Goldenberg 97)

Side effects :

Maternal →

Nausea
Heart burn
Vomiting
G.I.T bleeding .
Alteration in coagulation
Asthma
Hypertension (16) .

Fetal →

1. Constriction of ductus arteriosus (usually transient and respond to discontinuation of drug)(16-17-18-29).
2. Oligohydramnios (dose related and reversible) (18-24) .
3. Primary pulmonary hypertension (associated with prolonged > 48 hours indomethacin therapy) (25-26) .

4.Oxytocin Antagonists (Emergent management):

Oxytocin inhibitors offer a potential new therapeutic agent for treatment of preterm labor.Although the exact mechanism of action is not known , uterine oxytocin receptors and/or oxytocin may have etiologic roles in uterine hyperactivity in women with preterm labor. Studies of 2 oxytocin antagonists antocin and orally active non peptidyl oxytocin antagonist have suggested a high level of efficacy and few side effects(nausea and vomiting) with no fetal side effect (38-64-65).

5. Magnesium Sulfate:

Our study concentrates on $MgSO_4$ because it is the safe agent with limited tocolytic effectiveness .

Because of its Favorable safety profile, magnesium may be an especially useful choice when diagnosis of preterm labor is early and uncertain .

It is first used to prevent eclamptic seizures in 1906 by Hom in Germany .

In 1959 , the tocolytic properties of MgSO4 were initially described by Hall et al who noticed prolongation of labor in patients treated with MgSO4 .

It is particularly used in US (united states) as an alternative to beta-agonist.

Pharmacological mechanism:

The mechanism of tocolytic activity of $MgSO_4$ is unclear. In vitro studies of uterine muscle strips show reduced contractility in the presence of magnesium ion .It has been suggested that magnesium acts by competition with calcium either at the motor end plate reducing excitation or at the cell membrane, reducing calcium influx into the cell at depolarization. It has also been proposed that magnesium competitively binds with calcium storage site in the myometrial endoplasmic reticulum (Guiel- Bara et al 1985).

Excretion:

Magnesium is excreted by kidneys and after four hours about 50% of the infused dose is excreted in urine. In cases of oligouria or renal failure, the maintenance dose should be either reduced or discontinued and maternal plasma level monitored frequently .

Cruikshank et al demonstrated that urinary magnesium excretion increased 20 folds during MgSO4 infusion, 75% of the infused dose was excreted during the infusion and by 24 hours after the infusion, 90% would have been eliminated.Pitchard demonstrated that 99% of the magnesium in an intravenous bolus of 4 gm of MgSO4 was excreted within 24 hours.

Excretion of MgSO4 in breast milk

Cruikshank et al had demonstrated that intra-partum MgSO4 treatment lead to increase of breast milk-colostrum magnesium levels which provided to be only significant in the first 24 hours after discontinuation of the infusion .

Clinical use of MgSO4

MgSO4 is used as a Tocolytic agent in an initial 4 – 6 gm loading dose given intravenously over 15-20 min, followed by a continuous infusion rate of 2- 4 mg/h for the next 24 hours. Magnesium infusion rate should be titrated to maintain control of uterine activity while avoiding maternal toxicity. Frequent assessment of maternal peripheral reflexes, urinary output and non-invasive measures of oxygenation should be undertaken in all treated patients. The use of serum magnesium assays should be standardized for women on high doses, on prolonged high dose infusion and with underlying maternal renal disease(Besinger & Iannucci 1997).

Most physicians will avoid the toxicity that can be seen once the serum level exceeds 10 – 15 mg/dl by beginning to reduce the infusion rate once the serum level exceeds 8 mg/dl . (30)

Effects of MgSO4 on different organ-systems:

Effect on the nervous and cerebero-vascular systems:

These are different in the mechanisms and the sites of actions:

1. Some authors believe that its action is mainly peripheral at the neuromuscular junction with minimal or no central effects.
2. Others believe that the action is central with minimal neuromuscular blocking .
3. Calcium entry into neurons is regulated by specific excitatory amino acid receptor –linked channels.

The N-Methyl-D- Aspartate receptor is the best characteristic excitatory amino acid receptor subtype ؛ it's channel is being blocked by magnesium ions.

Cardio-vascular and respiratory effects:

1. Transient hypotensive effects are noted with bolus infusions Jame et al demonstrated a dose related reduction in systematic vascular resistance which confirms the vasodilator properties, this action is due to magnesium action on movement or translocation of calcium across the vascular membranes and intracellularly.
2. Increase or maintain cardiac out put and increase stroke volume.
3. Magnesium have a negative inotropic action, it inhibits the contractile force of isolated heart muscle.
4. Prolongation of atrial conduction time. (James et al).
5. Decrease maternal respiratory rate and may lead to pulmonary edema (the risk factors for pulmonary edema are anemia and multiple pregnancies) .
6. It does not cause significant changes in colloid osmotic pressure value until nearly 48 hours of continuous therapy . It was found consistently with lower values in women with preclampsia than those with preterm labor and

the use of corticosteroids with MgSO4 results in higher values than in patients not given steroids.

7. An increase in renal prostacyclin production was reported in patients with preterm labor after MgSO4 infusion .

8. MgSO4 possesses platelet antiaggregant properties and it prolongs bleeding time in pregnancy.

Effect on maternal calcium homeostasis:

Magnesium is intimately related to calcium homeostasis .Maternal hypocalcaemia following therapy with MgSO4 has been described. This is postulated to result from the interference with the synthesis or the release of parathyroid hormone.

Cruikshank et al showed that MgSO4 therapy depresses maternal calcium level by increasing urinary calcium loss and the resultant increase in parathyroid hormone output prevents more marked hypocalcaemia.

There were competitions between magnesium and calcium for the re-absorptive sites or the mechanisms of absorption in the nephrons (carney et al).

Effect on fetal heart rate (F.H.R)

The effects of MgSO4 on the F.H.R. are variable and have been a controversial issue. Niebyl noted that the decrease in long term variability was not associated with change in short term variability.Petrie et al reported an increase in both short and long term variability(37) .

After MgSo4 tocolysis 50% of fetuses had non reactive nonstress test and only 18% demonstrated fetal breathing movement. No effect was seen on fetal tone , movement , and amniotic fluid(63) .

Effects on the fetus and the newborn .

$MgSO_4$ may also be harmful to the fetus. Maternal levels rapidly equilibrate with fetal plasma, and the concentration in both of compartments is similar . $MgSO_4$ decrease fetal breathing then lead to decrease in total biophysical profile in full term fetuses.

Respiratory depression and hyporeflexia have been observed in newborn delivered to Mother under hyper-magnesia therapy, the new born requires 48-72 hours to excrete this magnesium load.

An apparent depression in serum calcium levels have been reported in fetuses of mothers treated with $MgSO_4$ (neonatal rickets) and unexplained demineralization of bones in the neonatal radiographs due to prolonged maternal tocolysis with $MgSO_4$.(more than 7 days)(34) .

A recent study had reported an association between magnesium tocolysis and reduction in intra- ventricular hemorrhage rates in treated infants (Wright et at 1990, E liott & Radin 1995 and Blair et al 1996).

Magnesium sulfate and anesthesia:

- At the neuromuscular junction magnesium decrease the presynaptic release of acetylcholine.
- Reduces sensitivity of the post junctional membrane (Motor end plate) and decreases excitability of the muscle fibers.
- Such neuromuscular blocking effects of magnesium will be potential .
- The non-depolarizing blocking agent and the depolarizing block of succinyl choline.
- Obstetric anesthesiologists aware of this fact and prescribe a smaller dosage of such medication when giving general anesthetics to patients on $MgSO_4$ therapy(10) .

Other effects:

Placental transfer: magnesium sulphate readily crosses the placenta, and fetal blood magnesium levels correlate with that of the mother, it usually occurs within two hours of MgSO4 infusion. Hallak et al had demonstrated that magnesium level did increase in fetal serum within one hour and in amniotic fluid within three hours after maternal intravenous administration. Prolonged maternal MgSO4 administration leads to accumulation of magnesium in the amniotic fluid.

Uterine activity

Stallworth et al found that MgSO4 caused transient mild decrease in frequency and significant change in the intensity of uterine contractions. Studies on isolated human maternal utero-placental arteries had demonstrated that infusion of MgSO4 increased uterine and placental blood flow.

Efficacy :

MgSO4 has been successfully used to inhibit preterm labor. A retrospective review by Elliot(9) showed that MgSO4 prevented delivery within 24 hours in 78%, within 48 hours in 76%, within 72 hors in 70% and to > 7 days in 51% of patients with intact membranes .

MgSO4 appeared to be more effective with less cervical dilation on admission .

Gestation was prolonged at least 48 hours in 87% of patient with cervical dilation < 2 cm , in 62% with cervical dilation of 3 – 5 cm , and 31% with cervical dilation of > 6 cm.

A cohort reported by Lifson et al showed that 90% of patients with cervical change treated with MgSO4 intravenous bolus of 4g, followed up by an infusion rate of 4gm /hr, or more remained undelivered at 3 days .

Inter-action of MgSO4 with nifedipine

Both are calcium channel blockers, they cause depression effect on blood pressure.

Nifedipine may potentiate the neuromuscular blockade effect and therefore may lead to toxicity of MgSO4 (6) .

Toxicity and side effects:

1. Loss of tendon (patella) reflexes, when the plasma level >5mmol/L it is the first sign of impending-toxicity (Ben Ami et al 1994).
2. Respiratory depression, occurs at levels > 6mmol/L (Digre et al 1990).
3. The most common side effects reported by patients include generalized flushing, nausea, vomiting, constipation, chest tightness, generalized muscle weakness and lethargy, double vision, slurred speech, somnolence which all usually occur at 3.8 –5 mmol/L.
4. Muscular paralysis and respiratory arrest occur when plasma level reaches 6.3-7.1 mmol/L
5. Cardiac arrest occurs when plasma level reaches 12.5 - 14.6 mmol/L.
6. Maternal death occurs at very high doses within minutes of infusion .
7. Injection abscess occurs due to intramuscular route of administration.

The antidote of magnesium toxicity is calcium gluconate 1mg in 10ml of 10% solution, given intravenously slowly to avoid hypotension or bradycardia.

Contraindication of MgSo4 therapy:

*Relative contraindication: (Ryan & Barss 1994):

These are :

1. Severe hemorrhage and abruption .
2. Sever pre-eclampsia.
3. Eclampsia.
4. Intrauterine fetal death .
5. Chorioamnionitis.
6. Pulmonary hypertension .
7. Maternal hyperthyroidism.
8. Sever intra uterine growth retardation .

*Absolute contraindication : These are:

1. Myasthenia gravis.
2. Heart muscle damage (conduction defects).

BOX 3

Magnesium Sulfate for the Treatment of Patients in Established Preterm Labor

Loading dose

Six grams (50 ml of 10% solution) added to 100 ml of normal saline IVPB in on less than 30 minutes.

Maintenance dose

Two to 3 g per hour depending on the response to therapy and the magnesium blood levels .

Monitor

- Urine output (should be at least 30 ml/hr) .
- Deep tendon reflexes (should be present and 1 + to 2 -) .
- Respiration rate (should be 15 per minute or more).
- Temperature .

Magnesium blood levels

Therapeutic ——→ 5-8 mEq/L

Loss of deep tendon reflexes ——→ 10 mEq/L

Respiratory failure . ——→ 12 mEq/L

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Material

1.Study group .

2.Control group .

***1. Study group*:**

Included 50 pregnant women with preterm labor with estimated gestational age between 24-34 weeks, calculated by ultrasound, last, menstrual period,& fetal quickening.

Selective criteria

1.Gestational age of patients between 24-34 weeks .

2.A live fetus.

3.The cervical dilation is ≤ 2cm and the effacement of the cervical canal is less than 80%.

Exclusive criteria

1.Non- reassuring fetal assessment .

2.Ruptured membranes .

3.Chronic medical illness of the mother , such as: renal failure , heart disease ,etc.....

4.Cervical dilatation more than ≥ 3cm (patient in active or advanced labor).

5.Congenital anomalies not compatible with life.

2. Control study:

The number of control group of women is similar to the study group with same selective criteria had been admitted to our hospital with preterm labor.

Int. J. Adv. Res. Biol. Sci. (2019). 6(3): 128-183

Study design :-

This is a prospective (case-control) study consist of 100 women attended to Al-Thawra Hospital from the 1st of Jan to the 30th of June 2005 with preterm labor .

Preterm labor was diagnosed when the patient admitted to labor room with obstetric estimation of gestational age based on menstrual history , timing of 1st feeling of fetal movement , fundal height and ultrasound examination .

The primary goal in this study was to stop uterine contraction in patients admitted to labor room with gestational age range from 24-34 weeks to get benefit of Corticosteroid injection to allow lung maturity of the fetus & to delay labor for 48hours. For these patients MgSo4 used to suppress uterine contraction had careful clinical assessment before starting MgSo4 and consent taken before starting infusion and patient is subjected to questionnaire and kept under observation in labor room .

Study Setting :

The obstetric unit in Al-Thawra General Hospital in Sana'a ,Yemen . It is the main referral hospital in Yemen . It accepts referral cases from other hospitals and clinics in Yemen .

The total number of patients admitted annually were 26397 , the total numbers of deliveries annually were 9830 .

Population :

100 women , 50 women with estimated gestational age range between 24-34 weeks calculated by last menstrual period , fetal movement or by ultrasound had preterm labor and MgSo4 used to suppress uterine contraction . The other group with the same selective criteria admitted to labor room with false labor pain or cervical dilatation ≥ 5cm &100% effacement(in active or advanced labor) or had contraindication for use of MgSo4 .

Variables :

Preterm labor : labor with gestational age < 37 weeks .

Parity : The no. of times a women has been pregnant .

Gestational age : Age of pregnancy or fetus estimated / weeks .

MgSo4 : Drug used in treatment of preterm labor and eclamptic seizures.

Clinical Presentation :

Regular uterine contraction 3 contractions per hour associated with cervical changes .

Out come :

Delaying Labor for 48 hours or discharge home after labor pain stopped .

Dosage of MgSO4:

- loading dose: 5gm in 100 ml of D.W 5% over 20-30 minutes.
- Maintenance dose: 2gm / hour until contraction are reduced to one or less / 10 minutes and no cervical changes then 1gm / hour for 24 hour.

During infusion attention was made for the following :

1.Flow sheet with hourly documentation of symptoms, chest examination, deep tendon reflexes, and total intake of fluid and output.

2.Limit I.V fluid to 100 ml/ hour.

3.Observation for signs of magnesium toxicity

-Loss of patellar reflexes.

-Respiratory rate < 15 / minute.

-Urine output. < 30 ml/ hour.

4.If the cervix was dilated up to 6cm MgSO4 infusion should be stopped.

If there is any complication appeared while patient on MgSO4 infusion it should be stopped immediately and the antidote of calcium gluconate must be given (1 gram given over 3 minutes) .

Control group :

The number of patients in control group are similar to that taken for study group.

The 50 cases of this group were between 24-34 weeks of gestation.

- All of them had been admitted to the labor room they are kept under observation with I.V hydration ,& sedation was given.

Results

Incidence

During the study period from the 1st of Jan. up to the 30th of June 2005 there were 5183 deliveries of which 239 had preterm labor with an incidence of (4.6%) see table (1) .

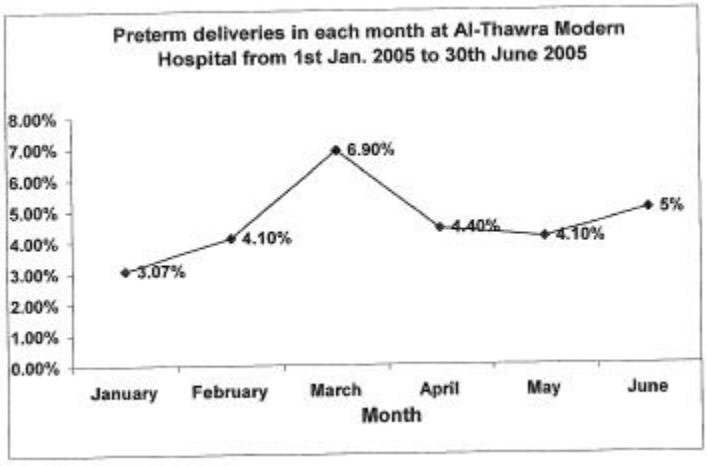
Table (1) incidence of preterm labor in 6 months period in Al-Thawra Hospital from the 1st of Jan. to the 30th of June 2005 .

Total No. Of deliveries	No. of preterm labor	Percentage
5183	239	4.6%

It was found that the highest No. of preterm labor was in June 48 patients (5%) while in Jan. 27 patients (3%) developed preterm labor *See table (2).

Table (2) The incidence of preterm labor each month during the study period in AL-Thawra hospital.

Month	Total No. of deliveries	No. of preterm labor	Percentage
January	879	27	3.07
February	792	33	4.1
March	803	56	6.9
April	814	36	4.4
May	935	39	4.1
June	960	48	5
Total	**5183**	**239**	**4.6**



Distribution according to the place of residence

It is the distribution of patients with preterm labor in study group and control group according to the place of residence , most of patients who were admitted to labor room in Al-Thawra Hospital with preterm labor came from urban area 36 patients (72%) of study group and 40 patients (80%) of control group while 14 patients (28%) of study group and 10 patients (20%) of control group came from rural area .

Table (3) Distribution of patients in study and control group according to the place of residence in AL-Thawra hospital.

Table (3)

Place of residence	No. of patients		Percentage	
	Study group	Control group	Study group	Control group
Urban	36	40	72%	80%
Rural	14	10	28%	20%
Total	50	50	100%	100%

Chi-square = 0.877 **P-value = 0.3489**

Distribution according to the chosen age of mother

This distribution shows that the younger patients (between15-30 years) exposed to preterm labor in both study and control group more than between 30-40 years of age .

Table (4) Distribution of study and control group who had preterm labor according to age in AL-Thawra hospital.

Table (4)

Age group (year)	No. of patients		Percentage	
	Study group	Control group	Study group	Control group
15-19	12	22	24%	44%
20-24	20	19	40%	38%
25-29	8	5	16%	10%
30-34	5	4	10%	8%
35-39	4	0	8%	0%
40	1	0	2%	0%
Total	50	50	100%	100%

Chi square = 8.770

P-value = 0.1186

Parity :

Most cases of preterm labor were found among those patients who were pregnant for the 1st time 20 patients (40%) of study group and 23 patients (46%) of control group while those with one previous pregnancy are 12 patients (24%) in the study group and 18 patients (36%) in the control group. Those with 2-5 previous pregnancies are 11 patients (22%) of study group & 7 patients (14%) of control group. Those with 6 pregnancies and above are 7 patients (14%) of study group and 2 patients (4%) of control group .

Table (5) Distribution of study and control group according to parity in AL-Thawra hospital.

Table (5)

parity	No. of patients		Percentage	
	Study group	Control group	Study group	Control group
0	20	23	40%	46%
1	12	18	24%	36%
2-5	11	7	22%	14%
6 and Above	7	2	14%	4%
Total	50	50	100%	100%

Chi square = 5.076

P-value = 0.1663

Previous Preterm deliveries :

Majority of patients with preterm labor in study and control group had no past history of preterm labor 42 patients(84%) of study group and 45 patients (90%) of control group while 8 patients (16%) of study group and 5 patients (10%) of control group are with previous 1-2 preterm labor and none had previous 3 or more preterm labor .

Table (6) Previous preterm delivery among study and control group in AL-Thawra hospital.

Table (6)

No. of previous preterm labor	No. of patients		Percentage	
	Study group	Control group	Study group	Control group
No preterm labor	42	45	84%	90%
1-2	8	5	16%	10%
3 or more	0	0	0	0
Total	50	50	100%	100%

Chi square = 0.796

P-value = 0.372

Previous abortion :

Majority of patients in study and control group with preterm labor had no history of previous abortion 40 patients(80%) of study group and 33 patients(66%) of control group while 9 patients(18%) of study group and 14 patients(28%) of control group had previous 1-3 abortions and for those with 4 and more abortion 1 patient (2%) of study group and 3 patients(6%) of control group .

Table (7) Previous abortion among study and control group with preterm labor in AL-Thawra hospital.

Table (7)

No. of perviuos abortion	No. of patients		Percentage	
	Study group	Control group	Study group	Control group
No abortion	40	33	80%	66%
1-3	9	14	18%	28%
4 or more	1	3	2%	6%
Total	50	50	100%	100%

Chi square = 2.758

P-value = 0.252

Gestational age :

Majority of patients with preterm labor of study group 20 patients(40%) are between 33-34 weeks while the majority of patients with preterm labor of control group 20 patients(40%) are between 29-32 weeks .

Table(8) Distribution according to gestational age among study and control group who had preterm labor in AL-Thawra hospital.

Table (8)

Gestational age	No. of patients		Percentage	
	Study group	Control group	Study group	Control group
24-28	13	14	26%	28%
29-32	17	20	34%	40%
33-34	20	16	40%	32%
Total	50	50	100%	100%

Chi square = 0.7247

P-value = 0.6960

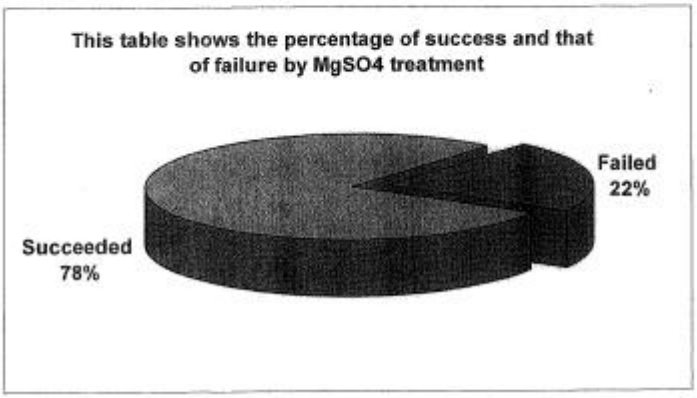
Success and failure rate :

From the 50 patients who received MgSo4 infusion to suppress uterine contractions 39 patients (78%) responded to MgSo4 and delivery was delayed more than 48 hours, while 11 patients (22%) not responded to MgSo4 infusion .

Table (9) No. of patients with PTL in study group who responded or not responded to treatment with MgSo4 in obstetric unit at AL-Thawra Hospital .

Table (9)

No. of cases	No. of patient	Percentage
Succeeded	39	78 %
Failed	11	22%
Total	**50**	**100%**



Antenatal care :

Majority of patients with study and control group were taken irregular antenatal care 27 patients(54%) of study group and 25 patients(50%) of control group, while those with regular A.N.C are 13 patients(26%) of study group and 22 patients(44%) of control group . Those with no ANC are 10 patients(20%) of study group and 3 patients(6%) of control group .

Table (10) No. of patients who were taken ANC in study and control group in AL-Thawra hospital.

Table (10)

A.N.C	No. of patients		Percentage	
	Study group	Control group	Study group	Control group
Regular	13	22	26%	44%
Irregular	27	25	54%	50%
None	10	3	20%	6%
Total	50	50	100%	100%

Chi square = 6.1604

P-value = 0.0459

Discussion

Preterm labor is an important problem in obstetric department. The incidence of preterm labor in white European was (5.7%) ,(9.4% - 10.2%)in Africans /Afro-Caribbean (Steer et al . 1995) ,(7.9%)in North Carolina (Bear et al 1995) and (10.6%) in North America. The incidence of preterm birth with spontaneous onset in the singleton varied between (4%-5%)in France (Blach More et al 1995).

In our study as shown in table (1) and (2) the incidence of preterm labor in our hospital during the period from the 1st of Jan. to the 30th of June 2005 is (4.6%) it is similar to the study done by (Blach More et al 1995).

*It was reported in Papiernik scoring system that the maternal age < 20 years is in high danger of preterm labor (Gonik and Creasy) . In our study,24% of the study group & 44% of the control group with preterm labor in the age range between 15-19 years, while 40% of the study group & 38% of the control group are in the age range between 20-24 years.

*Reports from British data indicates that the incidence of preterm labor is not increased if the maternal history reveals only 1st trimester abortion but it is increased significantly even if there is as few as one mid-trimester abortion (relative risk 2.3) but this is unhelpful in primi (31).

In our study we found that (more than 1/3)20 patients (40%) of the study group & 23 patients (46%) of the control group are nulliparous.In addition to that 8 patients (16%) of the study group & 5 patients (10%) of the control group had previous history of preterm labor, also 10 patients (20%) of the study group had previous spontaneous abortion while 17 patients (34%) of the control group had previous spontaneous abortion too.in our study we didn't found any relationship between preterm labor & 1st trimester abortion.

*Twins pregnancy is one of the multifactorial problem for preterm delivery(StevenGabbe).

Our study shows that 5 patients were having twins pregnancies between 29-32 weeks and all of them had delivered at preterm .

Prematurity is one of the predisposing factors of breech presentation , some authors consider preterm delivery as the commonest cause of breech presentation (Cunningham FG).

Our study shows that 26% of patients presented with breech presentation all of them delivered .

(Terrone et al 1999) did a dosing trial for MgSo4 in which they found the higher dose (2g versus 5g / h) achieved uterine tocolysis more rapidly . Elliott (1983) retrospective study , found that tocolysis with MgSo4 was successful , inexpensive and relatively non toxic . He reported 87% success when the cervix was dilated 2cm or less , but the period of delaying labor was as short as 48 hours.

Our study showed that using MgSo4 gave successful percentage of 78% as shown in table (9) in which patients had not delivered for more than 48 hrs .The patients who not responded to MgSo4 were 22% , all of them delivered in less than 48 hours .

*According to Dr. Brost serious side effects from MgSo4 tocolysis are rare and usually caused by improper dosage or monitoring of the patients (National review of medicine at Feb2005/vol 2 No. 4).

In our study from 50 patients , one patient (2%) developed generalized flushing , two patients (4%) had nausea & another one (2%) with chest tightness as side effects from MgSO4 tocolysis. And dose of Mgso4 was decreased. The possibility of labor should always be considered in any pregnant women presenting with abdominal pain , all too often the erroneous diagnosis of a U.T.I is applied . In study of 1040 acute presentations to the labor ward at Leeds General Infirmary in 1992 , (151) patients were thought to have U.T.I (Mac Dermott 1994).

- In our study only 9 patients (18%) from 50 patients of control group were diagnosed as U.T.I. .

*Keirse (1995) reported that women diagnosed to be preterm labor and allocated to a control group were not treated . 62% had not delivered after 48h and 34.5% went to term. In my control group 36% had false labor pain and they were discharged home with good general condition while other 64% delivered in less than 48 hours .

*Cox and associates 1990 , had randomized 156 women in preterm labor with intact membranes gave them either infusion of magnesium sulfate or normal saline . Magnesium sulfate 20% solution was begun using 4gm loading does followed by 2gm/hour infusion . If uterine contractions persisted after one hour, the infusion had been increased to 3gm/hour . N0 benefit for such therapy was found, and this method of tocolysis was abandoned at Parkland hospital .

In our study we had not increase the doses of magnesium sulfate to any of the patients of the study group.

Conclusion

Management of women in preterm labor remains a significant clinical and epidemiologic challenge-notably complicated by the difficulty of defining women with condition . For some women the symptoms mysteriously disappear for other women in whom symptoms do not subside .

The incidence of preterm delivery in Al-Thawra hospital during 6 months from the 1st of Jan. to the 30th of June 2005 was (4.6%). Tocolytic are likely to be beneficial if their use is combined with antenatal corticosteroid administration as a means to buy time to achieve maximal steroid effectiveness whilst undertaking if necessary , in utero transfer to a tertiary neonatal unit.We found in this study that MgSo4 is effective in prevention of preterm labor for > 48 hours in 78% of the patients .

The significant problems with the use of tocolytics remain because many patients requiring tocolysis arrive too late to benefit and many patients receiving tocolysis would not progress to delivery with no treatment .

Comment

Although the diagnosis and treatment of preterm labor are fraught with controversy , there are areas of consensus . Preconception counseling and early prenatal care that identifies and treats risk conditions can optimize pregnancy outcome . The physician must try to accurately date a patient pregnancy attempt to diagnose preterm labor at an early stage and make the appropriate management decision for the patient . This decision may include transfer to a tertiary site or management with appropriate consultation , fetal fibronectin a biochemical marker may be a useful diagnostic tool in the future ,but there are insufficient outcome data to justify its use at present .

Documented infections such as sexually transmitted diseases urinary tract infections and vaginosis should be treated . Tocolytic therapy should be used to delay delivery in order to administer corticosteroids . At present corticosteroid therapy is the only treatment shown to improve fetal survival and outcome .

Recommendations

The incidence of preterm delivery was 4.6% in AL-Thawra General Hospital ,Sana'a,Yemen through the period from the 1st of Jan. to the 30th of June/2005. Preterm delivery was due to multiple factors & according to that we recommend :

-Preconception counseling & early prenatal care (accurate dating of pregnancy , early diagnosis of preterm labor & proper management) in order to identify & treat risk conditions.

-Improvement of the antenatal care & the nursery care units(equipments , laboratories & facilities).

-Prevention & treatment of sexually transmitted diseases , U.T.I & vaginosis.

-MgSO4 & Dexamethason ampoules must be available in all hospitals especially in far cities to deal with patients until transferring them to central site.

-Improvement of the socio-economic & the educational state of the people.

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The Questionnaire

Case No.

Age:

Address: Rural( ), Urban( ).

Occupation:

Social status: Low( ), Middle( ),High( ).

Special habits: Smoking( ), Qat( ), None( ).

ANC: Regular( ), Irregular( ), None( ).

Obs.History:

- ***G….P…+…Alive( ).Dead( ), Abortion( )***
- ***GA…….weeks.***
- ***Previous history of PTL.***
- ***Previous history of abortion(2^{nd} trimester)***
  With D&C( ), without( )

Clinical Presentation:

1.Menstrual like cramps:

- ***Constant( ).***
- ***Comes &go( ).***
- ***Just above the pubic bone.***

2.Low dull backache:

- ***Constant( ). Comes & go( ).***

3.Abdominal cramping:

- ***With diarrhea( ), without( ).***

4.Increased or change in vaginal discharge:

- ***Mucoid( ), watery( ), bloody( ), light( ).***

5.Fluid leaking from the vagina(PROM).

- *Yes( ),NO( ).*

6.Uterine contractions > 3/hr.

- *Painful( ), painless( )*

Investigations:

1.Abdominal U/S:

- *Placenta Abruptio( ), P.P.( )*
- *Fetal Presentation *Longitudinal (Breech)( ),*
  (cephalic)( ),
  (Oblique)( ).
  **Transverse lie.*
- *Singleton( ),Twins( )*

2.P.V examination

Effacement(%),Dilatation( )cm.

Tocolytic I.V:

Loading dose( )

Maintenance dose( )

Side effect Yes( ), No( ).

Type of side effect ( ).

Outcome of recent admission:

1.Discharged well on I.V tocolytics

Yes( ) , No( ).

2.Delivery before 48hr.

Outcome of labor:

- *Alive( ),wt.( )*
- *Dead( ), wt.( )*

Sex( ).

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