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Magnesium Sulfate versus HCG (Human Chorionic Gonadotropin) in Suppression of Preterm Labor.

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Abstract:

Introduction: Preterm labor is defined as delivery before 37 completed weeks of pregnancy. Since 10% of total labors are preterm and 70% of infants' mortality is due to this problem, preterm labor is an important problem in obstetrics, midwifery and pediatrics. So that different treatments have been employed in order to suppress preterm labor from several years ago. Magnesium sulfate is often used as a first - line in suppressing of preterm labor, although its maternal and neonatal side effects are common, in best of conditions only 24-48 hours delays of labor, and randomized clinical trial studies have shown that in suppression of preterm labor it is as effective as placebo. On the other hand because of known ability of Human Chorionic Gonadotropin (HCG) in suppression of contractions in muscles detached from human myometer (in vitro), and safety of this drug in pregnancy, we take a decision that compare the ability of Magnesium Sulfate with HCG in suppression of preterm labor.

Materials and Methods: In this clinical trial study, 64 cases were chosen from pregnant women between the 24-34 weeks of pregnancy who were suffering from preterm contractions of uterus with intact amniotic sac and cervical dilatation of less than 4 cm. These women had referred to obstetric ward of Ali-Ebne-Abitalib Hospital, Zahedan, Iran during the years of 2004-6 and randomly were divided into two equal groups (32 cases in each group) In first group primarily 4 grams of Magnesium Sulfate (1 gram per minute) infused and then 2 grams per hour was continued. Whereas, in second group HCG was injected firstly 5000 units intramuscularly and then infused 20 units per minute. Treatments in both groups were continued to 12 hours after uterine contractions stoppage, during the treatments therapeutic effects as well as maternal conditions and complains were recorded in both groups. The results were analyzed by Chi square and T test with SPSS software, differentiation was regarded as significant if P value <0.05.

Results: The average duration between initiation of treatments and suppression of contractions of uterus in the first group who had received Magnesium Sulfate was 2.9 ± 0.5 hours, while in the second group that had received HCG was 3.14 ± 0.25 hours, so that differentiation of two groups from this point was non-significant ($p = 0.132$). Average rate of labor within 48 hours after beginning of treatment, in the first group was 13% while in second group it was 15% ($p = 0.223$), so that there was not significant differentiation between two group from this point too. Whereas, frequency of patients complaints due to side effects of medications in the first group was 100% while in second group was zero ($p < 0.0001$) which was significant.

Conclusion: HCG and Magnesium Sulfate in suppression of preterm labor have the same efficacy but since HCG has not any maternal and neonatal side effects, it is a good alternative in suppression of preterm labor.

Keywords: HCG, Magnesium Sulfate, Preterm labor.

Introduction:

American college of obstetrics and gynecology (ACOG) in 1995 has defined preterm labor as labors which take place after 20th week and before the 37th week of pregnancy. Preterm labor constitutes about 10% of the total labors, but since 70% of infants mortality is due to it, this problem is considered as one of the international indices in assessment of health condition in worldwide.⁽¹⁾

Various treatments have been employed to suppress preterm labor, but none has been able to delay delivery for more than 48 hours. But since the least benefit of this short delay is an opportunity for clinicians to administer glucocorticoids to mothers for acceleration of fetal lung maturation, reduction risk of neonatal intraventricular hemorrhage and necrotizing enterocolitis and therefore reduction of neonatal mortality, and on the other hand, this time give a chance to clinicians for refer the mother to a better and modern center possessing neonatal intensive care unit (NICU), All these treatments applied in order to suppress preterm labor by reducing contractions of uterus.^(1, 2)

Therefore preterm labor is a serious problem in mothers and childrens'health that there isn't a standard treatment for it yet. Corticosteroids, broad spectrum antibiotics and tocolytics are routine medications for suppress and support preterm labor.^(3, 4) Magnesium Sulfate has been used since 1960 in the United States in obstetrics for treatment of preterm labor.⁽⁵⁾ In Iran this drug is being used as first – line treatment for preterm labor too,

because it has been proven that Magnesium ion can suppress contraction of myometer by obstruction of calcium canals. But, some randomized studies have shown that Magnesium Sulfate in suppression of preterm labor has as effective as placebo.^(5, 6)

HCG in vitro by a type of system connected to gas can activate the plasma membrane of adenylate cyclase and this can reduce specific gap junctions of myometer cells and eventually decrease surface tension of intracellular calcium and keeping myometer in zero phase of labor and causing uterine relaxation.⁽⁷⁾

The power of HCG in suppression of preterm labor might be due to direct restrain of myometer responses by production of eicosanoids. HCG induces the production of eicosanoids and similar to prostacycline immediately cause loosening of myometer muscles.⁽⁹⁾

When Magnesium Sulfate is used in treatment of preterm labor, it can cause symptoms like: nausea, vomiting, hyperthermia, and hypotension and in some cases acute pulmonary edema and respiratory failure. At the same time, as a result of passage of magnesium ion into placenta different neonatal complications including muscular atony and restlessness are inevitable.⁽¹⁰⁾ We take a decision that compares the therapeutic effects of HCG and Magnesium Sulfate in suppression of preterm labor because:

1. With regard to proved ability of HCG in suppression of uterine contractions (in vitro) and safety use of this drug in pregnancy

2. Excess of maternal and neonatal Magnesium Sulfate side effects in suppression of preterm labor

3. Lack of Magnesium Sulfate priority to placebo in suppression of preterm labor in randomized studies.

Materials and Methods:

This study was a prospective and randomized clinical trial that was done in obstetrics ward of Ali-Ebne-Abitaleb hospital in Zahedan during 2004-6 on 64 women who were suffering from preterm labor pains. The criteria for the subjects to be enter in the study were: 4 uterine contractions per 20 minutes or 8 contractions per hour, 24-34th week of pregnancy, live single fetus, dilatation of less than 4 cm and intact amniotic sac. Excluding criteria were: existence of any background disease, hemorrhage, proof of any anomaly of uterus or fetus before or after of labor, chorioamniotitis, hypertension ($\geq 140/90$), dissatisfaction of patient in participation or continuation of study, trauma, use of tobacco and so on.

The patients were taking part in study consciously and voluntarily and were divided randomly to two equal groups (32 patients in each group). In both groups routine preterm labor tests including urinalysis, complete bed rest and infusion of 500 cc ringer lactate within half an hour was prescribed. Later, for treatment and rule out of false labor pains 10 mg of intramuscular morphine was administered in two groups. If one hour after morphine injection, contractions of uterus continued

in first group Magnesium Sulfate primarily 4 grams with speed of 1 gram per minute was infused and then 2 grams per hour in 5% glucose was infused. And in second group, at first 5000 units of HCG was injected intramuscularly and then 20 units per minute in 5% glucose was infused. Administration of drugs in both groups continued up to 12 hours after complete stoppage of contractions of uterus. Furthermore, within first groups during treatment every hour blood pressure, number of mother's breathing, reflexes of deep tendons, mother's urine output, heart rate of the fetus, were all checked and controlled and if they had any complaint due to drugs side effects, it would be recorded in her file. In second group vital signs of mothers and fetal heart rate were controlled every hour and any complaint would be recorded in her file too. This study was double blind and neither of patients and controller nurses knew about the type of drug.

The patients up to 24 hours after stoppage of uterus contractions were controlled in hospital and then discharged. However, in both groups in order to speed up maturation of fetus lung betamethazone with dosage of 12mg every 24 hours was prescribed for two days and in order to prevent any streptococcal infection in neonates in both groups 2 grams of ampicillin intravenously and every 6 hour was injected up to delivery time and in case preterm labor suppress, continued up to 48 hours.

In this research, the means of gathering data was interview and observation forms.

These forms including personal information and data related to study were filed during study and finally non – parametric data analyzed by chi-square and parametric data by T test in SPSS software and P value <0.05 was considered as significant.

Results:

The results of our study indicated that most factors in the Magnesium Sulfate

group and HCG group were the same including: parity of mothers, history of urinary infection, interval between previous and present delivery, history of preterm labor and abortion, duration and interval of contractions.

The results were analyzed in SPSS software by chi square and T test and Pvalue < 0.05 considered significant.

The following factors have not significant difference in two groups: mothers age, gestational ages, dilatation and effacement of cervix, urinary infection, time between start of treatment and suppression of contractions and labor within 48 hours (P>0.05).

But frequency of patients' complaints from tormenting side effects of drug have significant difference (P<0.05).

These findings have shown in following (Table 1 and 2).

Table 1: comparison of variables in two groups: Magnesium Sulfate and HCG

Variable	HCG	Magnesium Sulfate	P. value
Dilatation (cm)	2±0.23	1.9±0.38	0.148
Effacement (%)	42.5±4.9	41±5.8	0.019
Time between start of drug and suppress of contractions(hour)	3.14±0.25	2.9±0.5	0.123
Mother age (year)	25.5±0.8	26.1±0.9	0.552
Gestational Age (week)	30.8±0.3	31.6±0.5	0.235
Urinary infection (%)	25.5%	17.3%	0.311
Labor within 48 hours (%)	15	13	0.223
Complaints of Patients (%)	0	100	<0.0001

P value of <0.05 is considered significant.

Table 2: frequency of patients' complaints from side effects of drugs

Complaints of patients	Magnesium Sulfate	HCG
Headache	17	Nil
Dizziness	6	Nil
Thirst	48	Nil
Nausea and vomiting	30	Nil
Hyperthermia	53	Nil
Hyperthermia+ headache + vomiting	18	Nil
Nausea + headache	29	Nil
Number of patients	32	32

Discussion:

The findings of present research indicate that the ability of HCG in suppression of preterm labor is similar to Magnesium Sulfate however, maternal tormenting side effects of Magnesium Sulfate was 100% while it was nil for HCG.

In randomized studies Magnesium Sulfate was not different from placebo in suppression of preterm labor and its administration before 34th weeks of pregnancy increased rate of neonatal mortality.^(5,6) Mechanism of HCG in treatment of threatened abortion is reduction of resistance against arterial blood flow.^(7, 8)

HCG also reduces specific gap junctions of human myometer cells and its ability as tocolytic agent has been proved. Possible mechanism of HCG activity is enhancement of eicosanoids production that just like prostacyclines immediately loosens myometer muscles. Mechanism of action of HCG in treatment threatened abortion is to increase uteroplacental blood flow and it may be applied similarly in suppression of preterm labor.^(9, 10)

In a clinical trial study Magnesium Sulfate was compared with HCG in suppression of preterm labor in 2000 and its result was similarly to our study.⁽¹¹⁾

Preterm labor remains as the greatest risk for multiparity women.⁽¹³⁾ The risk of this problem is more for black race and if it occurs in one pregnancy, the chance of its occurrence in next pregnancies enhances

and usually happens at the same gestational age of other pregnancies.⁽¹⁴⁾

In some systematic review studies about management of preterm labor various drugs as tocolytics and corticosteroids are used from many years ago.^(12, 15, 16, 17, 18and 24)

In women who are multipar certain measures should be taken into account to prevent preterm labor for instance for 600 women with multiparity problem who had history of preterm labor for prevention of reoccurrence, hospitalization and bed rest was advised and in similar study clindamycin for prophylactic purpose was prescribed. Although, influences of the former remedies in reduction of predictors of preterm labor are limited and further comprehensive studies are required.^(19, 20, and 26)

In a meta-analysis that researchers selected from 20 RCTs about Ritodrine versus placebo and Ritodrine versus Magnesium Sulfate in treatment of preterm labor they concluded that, in treating of preterm labor Ritodrine can significantly prolong a short interval more quickly but with relatively more side effects than Magnesium Sulfate.⁽²¹⁾

In a study by review the available evidences regarding history, pharmacology, physiology, maternal/fetal effects, and efficacy of Magnesium Sulfate in pregnant women (data sources: the literatures in Medline was searched from 1966 through 2003), researchers concluded that using of Magnesium Sulfate

for treatment of preterm labor may be associated with increased infant mortality, so that they concluded Magnesium Sulfate should not be used in order to treatment of preterm labor.⁽²²⁾

In another study researchers concluded that, LH and HCG have multiple targets in the body, better understanding of nonclassical actions could lead to novel therapeutic applications of HCG such as prevention of threatened abortion and habitual abortion, preterm labor, etc.^(23, 25) In conclusion the efficacy of HCG and Magnesium Sulfate is the same in suppression of preterm labor. HCG has no maternal and neonatal side effects while hundred percent of mothers under treatment by Magnesium Sulfate were complaining from at least one tormenting side effect of the drug. Hence, HCG can be regarded as a proper substitute for Magnesium Sulfate in suppression of preterm labor.

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References:

1. Cunningham FG, Gant NF, Leveno KJ, Gilstrap LC. Williams Obstetrics. 22nd Ed, New York: McGraw- Hill; 2005. P: 856- 8
2. Lockwood Ci. Calcium- channel blockers in the management of preterm labor. The Lancet, 1997 350 (9088), 1339-1340.

3. James DK, Streer PJ, wether CP. High Risk Pregnancy. 20th ed, London: Saunders; 1999 P: 999- 1010.
4. Harrison TR, Braunwald E. Harrison principles of internal medicine 16th Ed. New York: Mc Grow- Hill; 2005. P: 221- 224
5. Bennett P, Edwards V. Use of Magnesium Sulfate in obstetrics. The Lancet, 1997 350 (9090), 1491.
6. Esmailpoor N, Shokrieh R, Magnesium Sulfate versus Placebo in treatment of preterm labor, J medical science of Gilan university, Iran 2001; (39): 72-77
7. Reshef F, Lei ZM, Rao Chv, Pridham DD, et al. The presence of gonadotropin receptors in non-Pregnant human uterus, human placenta, fetal membranes and deciduas. J Clin Endocrinol Metab, 1999 70, 421- 429.
8. Toth P, Gimes G, Paulin F, Rao Ch V. HCG treatment in early gestation: its impact on uterine blood flow and pregnancy outcome [abstract]. Fertil Steril, 1998 70, s46.
9. Chegini M, Lei ZM, Rao CV, Hansel W. Cellular distribution and cycle phase dependency of gonadotropin and eicosanoid binding sites in bovine corpora lutea. Biol report 1991; 45: 506- 13.
10. Kathleen P, Martindale W. The complete drug reference 32th Ed, Binghamton: pharmaceutical Press; 1999: 893.
11. Lorzadeh N, Dehnoory A, Momennasab M. HCG versus Magnesium Sulfate in prevention of preterm labor. J of obstetric & gynecol & infertility Iran 2003 (2): 12-19.
12. Berkman ND, Throp JM, Lohr KN, Carey TS, et al. Tocolytic treatment of the management of preterm labor a review of the evidence, Am J Gynecology 2003 Jun; 188 (6): 1648- 59
13. Washington H. Treatment of preterm Labor. Ob- Gyn J, 2004; 74 (1): 216- 227
14. Zachary A, Kristin A, Sarah E. Radical disparity in the frequency of recurrence of preterm labor AJOG 2007 Feb; 196 (2): 131- 132
15. Crowley P. Prophylactic corticosteroids for preterm birth. In: The Cochrane Library, Issue 1, 2003. Oxford: Update Software.
16. American Collage of Obstetrician and Gynecologists. ACOG practice bulletin no. 43. Management of preterm labor. Obstet Gynecol. 2003; 101: 1039- 1046

17. Scott A, Sullivan M, Roger N. Prediction and Prevention of Preterm Delivery in Multiple Gestations. *Clinical Obstet- Gyn J*, 2004; 74 (1): 203- 216
18. Morgan DJ, Taylor D. Late miscarriage and preterm birth after treatment with clindamycin. *BJOG* 2006 December; 113 (12): 1483
19. Crowther CA. Hospitalization and bed rest for multiple pregnancies. *Cochrane Database Syst Rev*. 2001; (1): CD 000110
20. Goldenberg RL, Iams JD, et al. What we have learned about the predictors of preterm birth. *Semin Perinatol*. 2003 Jun; 27 (3): 185-193.
21. Li X, Zhang Y, Shi Z. Ritodrine in the treatment of preterm labor: a Meta - analysis. *Indian J Med Res* 2005 Feb; 121 (2): 120-7
22. Azria E, Tsatsaris V, Goffinet F, Kaymen G, et al. Magnesium sulfate in obstetrics: current data. *J Gynecology Obstet Biol Repord (Paris)*. 2004 Oct; 33(6 pt 1): 510-7
23. Lei ZM, Mishra S, Zou W, et al. Targeted disruption of luteinizing hormone/human chorionic gonadotropin receptor gene. *Mol Endocrinol* 2001; 15: 184-200
24. Ables AZ, Romero AM, Chanhan SP. Use of calcium channel antagonists for preterm labor. *Obstetrics Gynecol Clin North Am* 2005 Sep; 32 (3): 519- 25
25. Louisville, Kentucky, USA. LH receptors: follicle and endometrium. *J Gynecol Obstet Biol Repord* 2002; 31: 1S7-1S11
26. D'ercole C, Bretelle F, Shojai R, Desbriere R, et al. Tocolysis: indications and contraindications, when to start and when to stop. *J Gynecol Obstet Biol Repord (Paris)*. 2002 Nov; 31 (7 Suppl): 5S84-95