IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 17, Issue 4 Ver. 11 (April. 2018), PP 62-65
www.iosrjournals.org

Comparison of Mifepristone and Misoprostol in Second Trimester Termination of Pregnancy

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Abstract: *Women with polycystic ovary syndrome (PCOS) are at higher risk of developing endometrial hyperplasia (EH). This study determined the prevalence of EH among women with infertility due to PCOS and assessed the predictive value of endometrial thickness (ET) measurement by trans-vaginal scan (TVS). This was a prospective study on infertile women with and without PCOS in which clinical data, hormonal profile, ET and endometrial biopsy (EB) for histopathological examination were collected. Thirty-seven women with PCOS and 23 women without PCOS presenting with infertility and/or abnormal uterine bleeding underwent TVS, hysteroscopy, laparoscopy and EB.*

OBJECTIVE(S)

- *We aim to assess and comparatively evaluate the safety and efficacy of misoprostol alone and mifepristone with misoprostol for second trimester termination of pregnancy.*
- *We aimed to evaluate the predictive value of amniotic fluid index (AFI) (<5) for adverse perinatal outcome in terms of cesarean section for fetal distress, birth weight, meconium staining, Apgar scores, and cord pH at birth.*

Date of Submission: 04-04-2018 Date of acceptance: 19-04-2018

I. Introduction

Modern obstetrics is concerned with the health and well-being of both the mother and the unborn child. Recognition of a fetus at risk for death or damage in utero, quantifying the risk, balancing the fetal risk against the risk of neonatal complications from immaturity, and determining the optimal time and mode of intervention are the cornerstones of modern perinatal medicine .Clinical estimation of amniotic fluid volume (AFV) is an important part of fetal assessment as variation in its amount has been related to a variety of pregnancy complications. Amniotic fluid provides a protective milieu for the growing fetus, cushioning it against mechanical and biological injury .Quantification of amniotic fluid is an important component of the biophysical profile in ultrasound evaluation of fetal well-being, especially in the third trimester. Antenatal tests use amniotic fluid volume as a fundamental assessment of chronic in utero stress. Ultrasound being a non-invasive test is ideal for application on a large scale and can be used frequently for repeat AFV determination in the case of suspected abnormalities. AFI of 5 cm or less is a predictor of adverse perinatal outcome in terms of meconium staining, cesarean section for fetal distress, birth weight, low Apgar scores, and cord pH

The second trimester termination of pregnancy is increasing because of increased determination of the sex linked genetic, metabolic disorders. Various surgical and medical methods have been tried for the second trimester MTP with varying success and induction abortion interval. Prostaglandins are associated with not only a high success rate but also with a short induction abortion interval. Misoprostol a newer synthetic prostaglandin E1 has proven its efficacy as an abortifacient for second trimester MTP since 1987. It is superior to all other available prostaglandins as it is stable at room temperature, requires no refrigeration, is cost effective, has fewer side effects, is a potent uterotonic and cervical ripening agent, free from bronchoconstrictive effect. It can be used by both the oral as well as vaginal route and in concurrence with other drugs as well. Mifepristone, (RU 486, a substitute 19- norethisterone derivative) by blocking the progesterone receptors causes estrogen dominance and results in intrauterine fetal death. At the same time it sensitizes the uterus to the activity of the prostaglandin. Thus, a combination of the two can significantly improve the efficacy of the misoprostol for the termination of second trimester termination of the pregnancy.

II. Materials And Methods

The present study was a prospective study carried out at the Sri Balaji Medical College and Hospital (SBMC), Chennai. The study participants included 200 booked antenatal women registered at SBMC Hospital with gestational age between 34 and 41 weeks, admitted for delivery over a 2-year duration from 2015 to 2017.

Inclusion criteria were women with a singleton, nonanomalous fetus with intact membranes at the time of ante partum testing. Women with premature rupture of membranes, with known fetal or chromosomal anomalies, gestational diabetes, Rh incompatibility, placental anomalies, and multiple pregnancies were excluded from the study. On admission, a detailed history was taken, and a clinical exam was performed and gestational age assessed. Amniotic fluid index was determined using the Phelan's technique within 7 days of delivery or at the onset of labor after informed written consent. Non stress test (NST) was performed for all patients. Women were divided into two groups based on their AFI (done within 7 days of delivery): Group 1—AFI < 5; Group 2—AFI > 5. A note was made of meconium staining of amniotic fluid, the ultimate mode of delivery, birth weight, Apgar score at 1 and 5 min, and cord pH measured at the time of birth.

The study was conducted on selected 200 cases came for second trimester termination of pregnancy from January 2015 to October 2017. A detailed history of the case regarding menstrual, obstetric, personal, medical with special reference to cardiovascular, respiratory, GIT, endocrinal disorder and coagulopathy was obtained. General and systemic examination of the cases was done. The patients with undiagnosed adnexal masses, hypertension, diabetes, jaundice, severe anemia, heavy smokers, adrenal insufficiency, coagulopathy, on corticosteroid therapy, porphyria, sickling, hemophilia, ITP were excluded from the study.

Proper counseling a written consent were obtained following which the cases were randomly divided in two groups of 100 each. Study group received 200 μg of mifepristone on admission. After 12 h in these cases 600 μg of misoprostol was inserted vaginally and thereafter 300 μg every 3 h until the abortion occurred or up to a maximum of 5 doses. Control group: the cases received misoprostol only in the same dose schedule. The cases were closely monitored for side effects if any, the onset of contraction, bleeding cervical dilatation each time before insertion of each misoprostol. Induction abortion interval, since the insertion of the first intravaginal tablet of misoprostol was noted down. The process is considered failed if abortion fails to occur in 15 h of the insertion of the first tablet of misoprostol, incomplete if part or whole of the placenta is retained. If placenta is retained for more than 2 h surgical evacuation was done. In case of failure another method medical or surgical was tried. Rh antibody was given to all the Rh negative cases at the end of the procedure. The data were analyzed.

III. Observations

Majority of the cases in both the groups were between 21 and 30 years of age. The mean gravidity of the cases was 3.62 ± 1.35 years in the study group and 2.9 ± 1.50 in the control group. The mean parity was 2.59 ± 1.34 and 1.79 ± 1.50 in the study and the control groups, respectively. The mean gestational age was 16.04 ± 2.57 and 19.03 ± 3.92 weeks in the study and the control groups respectively. 90% of the cases aborted within 9 h in the study group after the insertion of the first misoprostol tablet as against only 13% in the misoprostol alone group. All the cases in the study group aborted within 15 h in the study group as against only 79% in the control group. The mean induction abortion interval was 6.72 ± 2.26 h as compared to 12.29 ± 3.41 h in the control group. ($P < 0.001$) . Success rate was 100% in both the groups.

The abortion was complete in 95% of the study group while 90% in the control group. Need of other oxytocic for control of bleeding was in 14% of the control group as compared to 5% in the study group. ($P < 0.001$)

How was it calculated: Mean blood loss was 61.25 ± 19.67 and 67.25 ± 20.14 ml in the study and the control group, respectively ($P > 0.05$. Majority of the fetus in both the groups were aborted dead, 87 and 90%, in sac in 12% of the study group and 5% in the control group, respectively. The mean dose of the misoprostol required was significantly less in the study group 1,186 ± 291.64 μg as compared to 1,736 ± 320.20 μg in the control group, respectively ($P < 0.001$)

The side effects observed were mainly nausea, vomiting 10 and 14%, fever 18 and 23%, abdominal cramps 10 and 13%, flushing and diarrhea in 2% each in the study and control group, respectively

IV. Discussion

In the present study, meconium-stained liquor was present in 4 (16 %) of the patients in Group 1 and 26 (14.9 %) in Group 2, and the difference was not significant ($p = 0.881$). The cesarean section rate was higher in Group 1 with AFI ≤ 5, i.e., 56 % as compared to 35.4 % for Group 2, and the difference was statistically significant ($p = 0.047$). Cesarean section for fetal distress was also higher in patients with oligohydramnios as compared to the group with normal AFI (57.4 vs. 38.7 %) ($p = 0.048$).

In the current study, birth weight <2.5 kg was found in 14 (56 %) of the patients in Group 1 versus 38 (21.7 %) in Group 2, and the difference was statistically significant ($p = 0.001$In the present study, the 1-min Apgar score was <7 in 9 out 25 (36 %) babies in Group 1, whereas only 10.9 % babies in Group 2 had a 1-min Apgar score <7, and this difference was statistically significant ($p = 0.001$). However, the 5-min Apgar score <7 was almost equal in both the groups (4 vs. 3.4 %) ($p = 0.884$).In the present study, the cord pH at the time of birth, which is an objective marker of fetal distress, was <7.1 in one baby (4 %) in Group 1, whereas five babies

out of 175 (2.9 %) in Group 2 had cord pH < 7.1, which was not statistically significant. A study by Chauhan et al. also found no clear correlation between AFI and neonatal acidosis and it was stated that a multicentric study of sufficient power should be undertaken to demonstrate that low AFI is associated with umbilical artery pH < 7. A study by Morris et al. found a significant association between the number of babies with cord pH < 7 and AFI ≤ as 5.1 % versus 1.3 % for AFI > 5 (RR −3.3 and *p* value 0.01).

Misoprostol has proven its efficacy as an effective abortifacient for the second trimester termination of pregnancy. It is being successfully used through all the routes i.e. sublingual, oral and vaginal and in different regimens with the induction abortion interval varying from 12 h to as high as 33 h

Combination of mifepristone with misoprostol is now widely used method for first early first trimester pregnancy termination. Priming of the uterus with mifepristone makes it more sensitive to prostaglandins. It binds with the progesterone receptors and antagonizes the actions of progesterone on prostaglandin synthesis and metabolism resulting in increase in production and decreased deactivation of prostaglandins. It also induces cervical softening thus, enhancing the efficacy of the prostaglandins as an abortifacient.

The time interval between the insertion of the first tablet of misoprostol and start of contraction was significantly shorter in the study group 4.66 ± 2.03 as against 8.18 ± 2.68 in the misoprostol alone group ($P < 0.001$). The time interval between the insertion of the first tablet and the start of the bleeding was also significantly shorter in the study group 5.52 ± 2.13 h as compared to 9.98 ± 3.12 h in the control group. ($P < 0.001$). The induction abortion interval was significantly shorter 6.72 ± 2.26 h in the study group while it was 12.29 ± 3.41 h in the misoprostol alone group. ($P < 0.001$).

The success rate was 100% in the present study. The mean dose of misoprostol required was significantly less when used in combination with mifepristone as is also found in many other studies. The commonly observed side effects were nausea, vomiting, fever, abdominal cramp and diarrhea.

V. Conclusions

In the present study, antepartum oligohydramnios (AFI < 5) was associated with increased cesarean delivery, particularly for fetal distress. A significant correlation was found between oligohydramnios and low birth weight babies. However, there was no difference in perinatal outcome in terms of meconium staining, 5-min Apgar score, and cord pH between the two groups. When the secondary outcome was measured, significant correlation was found in terms of Non-reactive NST and admission to the NICU. Therefore, patients with severe oligohydramnios with AFI < 5 should undergo antepartum management in the form of *induction* of labor in order to improve their perinatal outcome.

ET ≥ 9.5 mm predicts EH in infertile women with PCOS, with a high degree of sensitivity and a moderate degree of specificity. In PCOS patients with oligomenorrhea or irregular cycles, the risk of EH is higher than women with regular cycles.

Second trimester termination of the pregnancy using combination of mifepristone and misoprostol is a safe, non invasive, highly cost effective method with a high success rate a short IAI. Pre-treatment with mifepristone adds to the effectiveness of the misoprostol as an abortifacient.

VI. Results

Out of the 200 women, the mean maternal age was 27.04 in Group 1 and 27.95 in Group 2, out of which, 17 (68 %) women were nulliparous in Group 1 and 103 (58.9 %) in Group 2. Gestational age was <37 weeks in 14 (56 %) in Group 1 as compared to 60 (34.3 %) in Group 2. Maternal weight gain during pregnancy was <10 kg in 9 (36 %) in Group 1 as compared to 15 (8.6 %) in Group 2. 18 (72 %) patients were induced in Group 1 as compared to 89 (50.9 %) in Group 2. Obstetric and perinatal outcomes were studied in both the groups.

4 (16 %) women in Group 1 and 26 (14.9 %) women in Group 2 had meconium-stained liquor. The difference was not statistically significant ($p = 0.881$). Cesarean section was performed in 14 (56 %) women in Group 1 as compared to 62 (35.4 %) in Group 2 ($p = 0.047$). Cesarean section for fetal distress was higher in women with oligohydramnios (57.1 %) as compared to women with AFI > 5 (38.7 %) ($p = 0.048$). Birth weight <2.5 kg was found in 14 (56 %) patients in Group 1 as compared to 38 (21.7 %) in Group 2. In Group 1, the Apgar score at 1 min was <7 in nine women (36 %) as compared to 19 (10.9 %) in Group 2 ($p = 0.001$). An Apgar score <7 at 5 min was noted in 1 (4 %) woman in Group 1 and 6 (3.4 %) women in Group 2 ($p = 0.884$). Cord pH < 7.1 was found in 1 (4 %) woman in Group 1 as compared to 5 (2.9 %) in Group 2 and the difference was not statistically significant ($p = 0.764$).

In Group 1, out of 25 women, 17 (68 %) had normal cardiotocography (CTG) and 5 (20 %) had pathological CTG. In Group 2, out of 175 patients, 146 (83.4 %) had a normal CTG and 9 (5.1 %) had pathological CTG. The rate of Pathological CTG in Group 1 was statistically significant .

The overall prevalence of EH was 23.3 % while in PCOS group: 18.3 %. The mean ET (14.8 mm) was significantly higher in patients with EH (t = -2.74, P value= 0.009). The lower value of ET among women with EH was 10 mm. A cut-off point of 9.5 mm was set. An ET of >9.5 mm had 92.9% sensitivity and 51.85% specificity for the presence of EH. Women with ET ≥ 9.5 mm were 1.28 times more at risk of EH than women with ET < 9.5 mm. Women with oligomenorrhea and irregular cycles were 5.5 and 13.7 times more at risk of EH compared to those with regular cycles, respectively. ET was positively correlated with insulin resistance (r = 0.439, P = 0.007).

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Dr. Mohana. T "Comparison of Mifepristone and Misoprostol in Second Trimester Termination of Pregnancy."IOSR Journal of Dental and Medical Sciences (IOSR-JDMS), vol. 17, no. 4, 2018, pp 62-65.