INTRODUCTION

Intra uterine fetal death (IUFD) affects the mother both physically and psychologically and entire family psychologically. In 2004 World Health Organization (WHO) defined IUFD as death prior to complete expulsion or extraction of a product of human conception from its mother, irrespective of duration of pregnancy and which is not an induced termination of pregnancy. (WHO, 2004) Currently WHO defines IUFD as all fetal deaths weighing 500gm or more occurring both during pregnancy (ante partum death) or during labor (intra partum death) (MacDorman, 2002). As definitions evolves constantly WHO defines IUFD as a baby born with no signs of life at or after 28 weeks of gestation for international comparison. (WHO, Maternal, newborn, child and adolescent health, 2016) Globally out of 2.6 million stillbirths in 2015 with a Still Birth Rate (SBR) of 18.4 per 1000 babies, the major occurred in the developing compared to developed Nations. India contributed highest for stillbirths. (Blencowe H, 2016).

Following an IUFD one can wait for spontaneous delivery or expectant management to avoid impending psychological and clinical complications that is when the need for induction arises. (WHO, Maternal, newborn, child and adolescent health, 2016). Usually spontaneous delivery ensues in 80-90% cases within 2 weeks of IUFD. (Silver TM, 2007)(RCOG, 2010)(Cabrol D, 1985) Induction of labor is defined as the process of artificially stimulating the uterus to start expulsion or extraction of a product of human conception from its mother, irrespective of duration of pregnancy or to fix time the birth of the baby, Health works workers (Convenience) & available health-care resources & infrastructure in the settings (Mozurkewich E, 2009) (NICE, 2008).

Though induction was described in Sao Paulo, Brazil in 1987 there are no standardized guidelines available for its application till date. Clinicians judge waiting for spontaneous labor to be of greater risk than shortening the duration of pregnancy with induction.

The IUFD itself does not constitute an indication for cesarean section (Mulher, 2000) therefore surgery should be reserved for specific conditions because of increased maternal morbidity without any fetal advantage. (ACOG, 2009) In the absence of emergency, priority must be labor induction with medicine and finishing the pregnancy through the vaginal route (Silver RM, 2010) Deciding for the surgical induction depends fetal and obstetric conditions taking psychological impact on the mother into consideration (Habek D, 2008)(Steel A, 2009).

Royal College of obstetricians & Gynaecologists (RCOG) in its Green-top Guideline No. 53 recommends a combination of drugs for IUFD which is also endorsed by the National Institute for health and care excellence(NICE) guidelines (Silver TM, 2007) (Cabrol D, 1985) Whereas WHO recommends single drug usage. There is lack of uniformity in use of misoprostol in specific trimesters and route of administration, taking side effects too into consideration (Eng N, 1997) (Jain J, 1996)Nevertheless, the current evidence has concluded that the most appropriate route of administration is vaginal (Wagaarachchi PT, 2002). Hence the ideal drug for the termination of pregnancy in cases of IUFD should not only be effective and safe, but also cost effective. With this base Knowledge we aimed to evaluate safety, tolerance and efficacy of combination regimen of mifepristone and misoprostol with conventional use of misoprostol alone.

AIMS & OBJECTIVES

Aim of my study is to evaluate safety, tolerance and efficacy of combination regimen of mifepristone and misoprostol with conventional use of misoprostol alone.
This Prospective interventional study was conducted in Department of Obstetrics and Gynecology at a Tertiary care hospital, IMS&M Hospital, Bhubaneswar for 2 years between August 2018-2020. Purposive and consecutive sampling was adopted among patients with IUFD as study involved single investigator without specific sample size calculation. Proper randomization was not executed for the same reasons. Hence the principle investigator provided Tab. Mifepristone 200mg orally followed by Tab. Misoprostol vaginally after 24hrs and others administered Tab. Misoprostol vaginally for two years. At the end of two years 25 from each group was taken for analysis. All Women with IUFD attending outpatient department, Gravid up to 4 during study period, >24 week period of gestation, Not in labor (no regular contractions or unfavorable cervix) & willing for medical management were taken as study participants. Patients with allergy to prostaglandins, asthma, glaucoma, multiple gestation and previous uterine scar were excluded.

As per RCOG guidelines dose of misoprostol was given in both groups as follows. Routine investigations & procedures for mother was done, As per RCOG guidelines dose of misoprostol was given in both groups as follows. Routine investigations & procedures for mother was done, As per RCOG guidelines dose of misoprostol was given in both groups as follows. Routine investigations & procedures for mother was done, As per RCOG guidelines dose of misoprostol was given in both groups as follows. Routine investigations & procedures for mother was done, As per RCOG guidelines dose of misoprostol was given in both groups as follows. Routine investigations & procedures for mother was done, As per RCOG guidelines dose of misoprostol was given in both groups as follows. Routine investigations & procedures for mother was done, As per RCOG guidelines dose of misoprostol was given in both groups as follows. Routine investigations & procedures for mother was done, As per RCOG guidelines dose of misoprostol was given in both groups as follows. Routine investigations & procedures for mother was done, As per RCOG guidelines dose of misoprostol was given in both groups as follows. Routine investigations & procedures for mother was done, As per RCOG guidelines dose of misoprostol was given in both groups as follows. Routine investigations & procedures for mother was done, As per RCOG guidelines dose of misoprostol was given in both groups as follows. Routine investigations & procedures for mother was done, As per RCOG guidelines dose of misoprostol was given in both groups as follows. Routine investigations & procedures for mother was done, As per RCOG guidelines dose of misoprostol was given in both groups as follows. Routine investigations & procedures for mother was done.

Table 1: Comparison Of Characteristics Categorically Among Study Participants In Group A & Group B.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>GROUP A</th>
<th>GROUP B</th>
<th>χ²</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age group n (%)</td>
<td>Misoprostol only</td>
<td>Mifepristone &amp; Misoprostol</td>
<td>Chisquare</td>
<td></td>
</tr>
<tr>
<td>&lt;20 years</td>
<td>0</td>
<td>0</td>
<td>2.37</td>
<td>0.66</td>
</tr>
<tr>
<td>20 – 25 years</td>
<td>9 (36%)</td>
<td>8 (32%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>26 – 30 years</td>
<td>7 (28%)</td>
<td>9 (36%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>31 – 35 years</td>
<td>8 (32%)</td>
<td>1 (28%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>36 – 40 years</td>
<td>4 (16%)</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parity n (%)</td>
<td>G1</td>
<td>G2</td>
<td>χ²</td>
<td>P value</td>
</tr>
<tr>
<td></td>
<td>17 (68%)</td>
<td>17 (68%)</td>
<td>1.03</td>
<td>0.79</td>
</tr>
</tbody>
</table>

RESULTS

In this study over 2 years, Fifty (N=50) participants with IUFD were included. The comparison with regard to patient's characteristics was done in both Group A (n=25) & B (n=25) socially and clinically, as it's a comparative study. Similarity was found in patient's characteristics with respect to Age, Parity, Period of gestation, along with amount of drug used (Systoicin & Misoprostol) across the groups when expressed categorically as in Table 1. Mean age of the participants was approximately 28 years; similarly proportion of primigravida (68%) was higher in both groups compared to multigravida as shown in Table 2.

Table 2: Comparison Of Characteristics Categorically Among Study Participants In Group A & Group B.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>GROUP A</th>
<th>GROUP B</th>
<th>χ²</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age(years)</td>
<td>28.7(±4.7)</td>
<td>27.3(±4.5)</td>
<td>0.62</td>
<td></td>
</tr>
<tr>
<td>POG</td>
<td>33.7(±4.6)</td>
<td>33.6(±4.6)</td>
<td>0.09</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>23.14(±1.3)</td>
<td>23.55(±1.3)</td>
<td>0.54</td>
<td></td>
</tr>
<tr>
<td>Hb(g/dl)</td>
<td>11.08(±1.2)</td>
<td>11.1(±1.2)</td>
<td>0.03*</td>
<td></td>
</tr>
<tr>
<td>Baby weight(grams)</td>
<td>1092.6(±232.5)</td>
<td>1082.4(±890.4)</td>
<td>0.39</td>
<td></td>
</tr>
<tr>
<td>Bishop score</td>
<td>3.8(±1.8)</td>
<td>5.6(±1.2)</td>
<td>0.62</td>
<td></td>
</tr>
<tr>
<td>Induction delivery interval(hours)</td>
<td>18.8(±10.1)</td>
<td>13.6(±6.5)</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>Induction delivery time VS Gravida</td>
<td>14.8(±7.2)</td>
<td>14.8(±7.2)</td>
<td>0.09</td>
<td></td>
</tr>
<tr>
<td>Primi gravida</td>
<td>n=17</td>
<td>n=19</td>
<td>18.9(±6.2)</td>
<td>0.09</td>
</tr>
<tr>
<td>Multigravida</td>
<td>n=33</td>
<td>n=31</td>
<td>11.68(±1.2)</td>
<td>0.12</td>
</tr>
</tbody>
</table>

Pvalue <0.05 is considered Significant.

As per the main objective we tried to assess the tolerance to drugs among both groups. Chi square test was applied and there was significant difference between two groups with regard to the following characteristics, Induction delivery interval & Hemoglobin (Hb) concentration.
primigravida with a short duration of induction 14.8 (±7.2) as compared to other group but difference was not found significant statistically (P value = 0.09).

DISCUSSION:
Several induction methods following late IUFD have been described. A variety of routes of administration of prostaglandin analogues including PG E and PG F have been used with success. (Meckstroth KR, 2006) (El-Rafey H, 1995) Studies have confirmed the benefits of misoprostol and combinations with mifepristone in second and first trimesters with mifepristone respectively. (Scher J, 1980) (Filsheh GM, 1971) However, there are limited studies using a combined regimen for induction of labor in IUFD. In this study no new regimen was designed specifically, we tried to compare those already described in the literature and tried to capture how well these published regimens perform in India among women undergoing induction for IUFD.

Age in Years
Patients belonged to age group of 19 to 40 years, majority of the patients were of 20-25 years (68%). Mean age in Group A, B was 28.72 years 27.36years respectively. Similar age distribution was in other studies (Cabrol D e a., 1990) (Urquhart DR, 1990)

Parity
There was a uniform distribution of primigravida and multigravida patients in both the groups, however most were primigravida. Similar representation was in study with tenfold higher participant's (Ashok PW, 1999)

Gestational age
The mean gestational age in Group A and B was 33.76 weeks, 33.60 weeks. However lower mean gestational age was found in studies which could be attributed to very early induction (Cabrol D e a., 1990) (Ashok PW, 1999)

Side effects:
In Group A and Group B, 84%, 92% of patients had nil side effects. However abdominal cramps, nausea, vomiting, diarrhea was the utmost side effects occurred in both groups. Side effects were similar in other studies (Nathinne Prachasilpchai, 2006)


Based on drug dosage the mean induction to delivery interval was relatively shorter with increased dosage (7 hrs with 400mg vaginal/oral misoprostol with mifepristone tablets) (Fairley, 2005). But those patients had 15% higher incidence of gastrointestinal side effects. Emphasizing the fact while using combined regimen there should be a fine balance between the dose, route of administration, induction to delivery interval and side effects as in current study for optimum results.

Complications
Serious complications like uterine rupture were not seen in the present study. In 4% of cases retained placenta was another complication encountered and managed, similar to other studies (Paul A. le Roux, 2001)

Prostaglandins

Serious complications like uterine rupture were not seen in the present study. Induction delivery interval was significantly shorter in Mifepristone & Misoprostol group compared to Misoprostol only group and the association was more in primigravida than multigravida. The combination of mifepristone and misoprostol is a safe and effective method for labor induction following IUFD. The induction to delivery interval is shorter with a better side effects profile in combined regimen.

REFERENCES
37. Wagaarachchi PT, A. P. (2002). Medical management of late intraterine death using a randomized control trial. Limited sample size was adopted as it’s a single investigator study. If limitations are rectified, study conclusions would hold a stronger validation.


