FIRST TRIMESTER TERMINATION OF PREGNANCY WITH MISOPROSTOL ALONE COMPARED WITH SURGICAL MANUAL VACUUM ASPIRATION: A RANDOMISED, CONTROLLED TRIAL.

BY

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## INTRODUCTION (1)

- **Worldwide:**
  - Almost all the 21.6 million of unsafe abortions in 2008 occurred in developing countries. *(WHO. Unsafe abortion: global estimate of incidence and associated mortalities. 6th edition, 2011)*

- **In South Africa:**
  - Unsafe abortion ranks 4th among the 5 leading cause of maternal mortality.
  - *(DOH. Saving Mothers Report 2008-2010.)*

- To improve access to safe abortion in South Africa:
  - CTOP act of 1996.
  - Medical abortion introduced in 2001 by medicine control council
  - Amendment of the CTOP act in 2004.
INTRODUCTION (2)

• 2 methods of abortion: surgical and medical.
  • MVA is safe, well suited for low resource settings with high efficacy (95%-97% complete abortion rate) (WHO technical report 2003)
  • Medical abortion with Mifepristone + Misoprostol is safe with high efficacy (95.7%) H Hamoda & A Templeton. Best Practice & Research Clinical Obstetrics and Gynaecology 24 (2010).

• The constraint of high cost and non availability limits the use of the Mifepristone regime in the public health sector of South Africa.
• On the other hand Misoprostol alone, which is cheap, thermo stable and a potential alternative, has not been demonstrated widely in developing countries to offer credible benefits.
INTRODUCTION (3)

- Buccal Misoprostol alone has not been compared with MVA in a RCT.
- Buccal route is more convenient to administer compared with the vaginal route.
- Misoprostol pharmacokinetics showed that:
  - Buccal route has equal uterine response as vaginal route
  - With less serum peak plasma conc: hence less side effect

Peak serum conc: /time
Vaginal 400pg/ml at 60mins
Buccal 200pg/ml at 60mins

Peak Uterine response
Vaginal 1200AU at 4 hours
Buccal 1200AU at 4 hours
Plateau at peak longer with Buccal.

HYPOTHESIS

In the light of these evidence we compared the efficacy and safety of 2 doses of Buccal Misoprostol with MVA in a hospital based, parallel treatment group, non inferiority RCT.

Assuming a 5% difference in efficacy to be significant clinically, a sample of 516 participants will have 80% power to detect this difference in efficacy, based on a 2-sided test of significance, with an alpha error of 0.05 and a beta error of 0.2, assuming 88% success rate for the medical arm, and 98% success rate for the control arm.

OBJECTIVES

Primary objective: compare the success rate of first trimester abortion using misoprostol alone with the success rate of first trimester abortion using manual vacuum aspiration.

Secondary objective: compare the side effects of using misoprostol alone with the side effects of using manual vacuum aspiration during first trimester abortion.

550 participants simply randomised into 2 groups in 1:1 allocation ratio using two sets of sealed and mixed opaque envelopes for allocation concealment.

We included:
- Healthy women seeking termination of pregnancy.
- Singleton Pregnancy less than or equal to 12 completed weeks (84 days) as determined by ultrasound dating of the pregnancy.
- Informed consent to undergo either medical or surgical abortion.
- Consent to be randomised into either of the 2 arms of the abortion procedure.
- Able to come back if there is urgent need.
- Women with Previously scarred uterus (caesarean section) were also included.

We excluded women with:
- Ectopic pregnancy;
- Anaemia (haemoglobin < 10 g %);
- Haemolytic disorders; or
- Pelvic inflammatory disease.
- Allergy to misoprostol
- Inability to attend follow-up visit.
Figure 1: TRIAL FLOW-CHART OF ELIGIBILITY & RANDOMIZATION

- Assessed for eligibility (n=618)
  - Did not meet inclusion criteria (n=42)
    - Declined (n=26)
  - Randomized (n=550)
    - Allocated to medical abortion arm (n=275) all had medical abortion.
      - Lost to follow up (n=5)
        - Discontinued intervention requested surgical evacuation on day 10 (n=1)
      - Analyzed (n=270)
    - Allocated to surgical abortion arm (n=275) all had surgical abortion.
      - Lost to follow up (n=3)
      - Analyzed (n=272)
**GROUP 1**
Gest age (CRL), Hb, Rh, RPR, STI prophylaxis
Buccal Misoprostol 800μg x 2 doses 4hrs apart
1g paracetamol orally before the 2nd dose of misoprostol.
Observe till close of clinic
Weekly clinical review x 3(βhcg, biendometrial thickness)
Repeat MVA done, if no abortion, incomplete abortion at 3 wks, severe bleeding, patient’s request, infection.
Bleeding, pain-score, Use of Analgesia, presence of infection, assessed.
Last review at return of menstruation.

**GROUP 2 (MVA group)**
- Gest age (CRL), Hb, Rh, RPR, STI prophylaxis
- Cervical priming with 1 (Misoprostol group)
  - Misoprostol 200μg sublingual.
  - 75mg diclofenac IMI 30 minutes before procedure.
  - MVA 4 hours after cervical priming.
  - Weekly follow up till return of menstruation.
  - MVA done, if no abortion, incomplete abortion at 3 wks, severe bleeding, patient’s request, infection.
  - Pain score, further use of analgesia, amount and duration of bleeding, presence of infection assessed.
  - Last review at return of menstruation.

**Incomplete abortion criteria:**
- bleeding after 21 days (97.5% senst. 75% spec.)
- biendometrial thickness >15mm (94.1% sens. 75% spec)
- serum βhcg >500iu (97.1% sens. 62.5% spec)
Table 1: Distribution of age, parity, gestational age and haemoglobin values before Termination of Pregnancy between the two arms of the study.

<table>
<thead>
<tr>
<th></th>
<th>AGE (YEARS)</th>
<th>PARITY</th>
<th>GESTATION (DAYS)</th>
<th>HAEMOGLOBIN (gm/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grp1 n=275</td>
<td>Grp 2 n=275</td>
<td>Grp1 n=275</td>
<td>Grp 2 n=275</td>
</tr>
<tr>
<td>Median</td>
<td>24</td>
<td>25</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Percentiles</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25th</td>
<td>21</td>
<td>20</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>50th</td>
<td>24</td>
<td>25</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>75th</td>
<td>30</td>
<td>32</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Minimum</td>
<td>14</td>
<td>15</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Maximum</td>
<td>44</td>
<td>43</td>
<td>5</td>
<td>6</td>
</tr>
</tbody>
</table>

Mann-Whitney U Test (2-tailed) p-value

<table>
<thead>
<tr>
<th></th>
<th>Grp1 n=275</th>
<th>Grp 2 n=275</th>
<th>Grp1 n=275</th>
<th>Grp 2 n=275</th>
<th>Grp 1 n=275</th>
<th>Grp 2 n=275</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.355</td>
<td>0.578</td>
<td>0.992</td>
<td>0.563</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Key: Grp 1 = medical arm of the study, Grp 2 = surgical arm of the study.
Table 2: Distribution of women with previous caesarean section, previous induced abortion and use of contraception between the two arms of the study.

<table>
<thead>
<tr>
<th></th>
<th>PREVIOUS CAESAREAN SECTION</th>
<th>PREVIOUS INDUCED ABORTION</th>
<th>USE OF CONTRACEPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group 1 n=275</td>
<td>Group 2 n=275</td>
<td>Group1 n=275</td>
</tr>
<tr>
<td>count</td>
<td>count</td>
<td>count</td>
<td>count</td>
</tr>
<tr>
<td>YES</td>
<td>13</td>
<td>10</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>4.7</td>
<td>3.6</td>
<td>5.8</td>
</tr>
<tr>
<td>NO</td>
<td>262</td>
<td>265</td>
<td>259</td>
</tr>
<tr>
<td></td>
<td>95.3</td>
<td>96.4</td>
<td>94.2</td>
</tr>
<tr>
<td>Odds Ratio</td>
<td>1.31</td>
<td>0.76</td>
<td>0.62</td>
</tr>
<tr>
<td>Chi-square test</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>0.671</td>
<td></td>
<td>0.194</td>
</tr>
</tbody>
</table>

*Key: Group 1 = medical arm of the study, Group 2= surgical arm of the study.*
### Table 3: Comparison of abortion success between the two arms of the study

<table>
<thead>
<tr>
<th>ABORTION OUTCOME</th>
<th>TREATMENT GROUPS [GROUP 1 = MEDICAL ARM; GROUP 2 = SURGICAL ARM]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>GROUP 1 [N = 270]</td>
</tr>
<tr>
<td><strong>CASES</strong></td>
<td><strong>%</strong></td>
</tr>
<tr>
<td>COMPLETE</td>
<td>258</td>
</tr>
<tr>
<td>ABORTION</td>
<td>95.6% (3%)</td>
</tr>
<tr>
<td>FAILED ABORTION</td>
<td>12 (8)</td>
</tr>
<tr>
<td></td>
<td>4.4% (3%)</td>
</tr>
</tbody>
</table>

- No RCT has compared Buccal Misoprostol with MVA.

- **Prasad S et-al.**
  
  (Fertility & Sterility 2009; 91:28-31)
  
  - Misoprostol group – 94.2% Vs 95.5% in Vacuum aspiration group

- **N Ngoc et-al.**
  
  
  - Mifepristone + buccal Misoprostol 96.4%
  
  - Buccal Misoprostol alone 24hrs apart 75.1%

- Synergistic effect of 2 doses of Misoprostol 4 Hrs apart

- Longer Follow up period.

- New FIGO Guidelines uses 2 doses of buccal Misoprostol 3 Hrs apart – 98% efficac
  
100% complete abortion at gest. 42 days or less

Prasad S et-al : found similar trends
(Fertility & Sterility, 2009; 91: 28-31)

Zikopoulos et-al : < 42 days gest – 96.3%
42 -56 days - 86.3%
(Hum. Rep 2002; 17: 3079-83)

Chelly dallenda et-al 63-84 days - 77.4% Vs.
95.2% (for this study)

Continuation of preg. more at below 6wks gest. in surgical abortion.
(RCOG guideline number 7 Sept. 2004)

Continuing pregnancy rate of 0.4%

Planned parenthood federation of America

Crenin & Edward

Ashoek et-al (UK series) – 0.10%
(BJOG 2002; 109: 1281-9)
Table 4: Comparison of the side effects between the arms of the study.

<table>
<thead>
<tr>
<th>OUTCOME</th>
<th>INFECTION</th>
<th>SEVERE PAIN</th>
<th>SEVERE BLEEDING</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group 1 n=270</td>
<td>Group 2 n=272</td>
<td>Group 1 n=270</td>
</tr>
<tr>
<td>YES</td>
<td>count</td>
<td>%</td>
<td>count</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>1.1</td>
<td>4</td>
</tr>
<tr>
<td>NO</td>
<td>267</td>
<td>98.9</td>
<td>268</td>
</tr>
<tr>
<td>Relative Risk (Odds Ratio)</td>
<td>0.73 (95% CI, 0.17 - 3.5)</td>
<td>0.11 (95% CI, 0.01 – 0.2 )</td>
<td>6.17, (95% CI, 3.17 – 12.23)</td>
</tr>
<tr>
<td>Pearson’s Chi-square test (p-value)</td>
<td>0.711</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

**Key:** Group 1 = medical abortion arm. Group 2 = surgical abortion arm.

Bleeding: severe bleeding more in the medical group. No participant required blood transfusion. (long time to complete/unattended procedure)

Severe pain more in surgical arm. (para-cervical block not used. Limitation of space and personnel could not allow for use of conscious sedation)

Infection rate: low in both groups.
- Shannon C et al - 0.92% (Contraception 2004; 70: 183-90)
- RCOG: 10% (RCOG guideline number 7 Sept. 2004)
TABLE 5: Side effects of misoprostol in the medical abortion arm.

<table>
<thead>
<tr>
<th>OUTCOME</th>
<th>VOMITING</th>
<th>DIARRHOEA</th>
<th>SHIVERING</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>count</td>
<td>percentage</td>
<td>count</td>
</tr>
<tr>
<td>YES</td>
<td>16</td>
<td>5.9% (23%)*</td>
<td>52</td>
</tr>
<tr>
<td>NO</td>
<td>254</td>
<td>94.1</td>
<td>218</td>
</tr>
<tr>
<td>RISK / ODDS</td>
<td>0.26 (95% CI 0.14 -0.38)</td>
<td>0.19</td>
<td>0.08 – 0.32</td>
</tr>
<tr>
<td>Chi-square test: p-value</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Key: p values were calculated using reported values from review by Hamoda H and Templeton A. (Bet practice & research clinical obstetrics and Gynaecology 2010) as expected values. * expected percentages are enclosed in brackets.
Medical abortion with two doses of Buccal misoprostol alone is safe and has a success rate comparable with surgical abortion using manual vacuum aspiration in first trimester pregnancy termination.

Study limitations are:

Blinding difficult.  
induction to completion of abortion difficult to assess,  
Study not powered for side-effects like rupture and mortality

Impact on clinical practice:

There is a choice without mifepristone  
While we await wide availability of mifepristone, medical TOP at primary care level is feasible with Buccal Misoprostol. This will improve access to safe abortion.  
However back up services with manual vacuum aspiration should be provided for failed medical abortion.
THANK U.