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Second trimester abortion using isosorbide mononitrate in addition to gemeprost compared with gemeprost alone: A double-blind randomized, placebo-controlled multicenter trial

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Objective: We aimed to determine whether second-trimester abortion using isosorbide mononitrate (IMN) in addition to gemeprost is more effective and reduces side effects compared with gemeprost alone.

Study design: Eighty women who were age 13 to 23 weeks' gestation were randomly assigned to receive per vaginam either IMN 40 mg (group 1, 40 women) or placebo (group 2, 40 women) in addition to gemeprost 1 mg up to 3 times daily 3 hours apart for 2 days. Analysis of variance, a χ^2 test, and a multivariate analysis were performed.

Results: Of the 72 women analyzed, 68% (group 1) and 38% (group 2) underwent abortion within day 1 ($P < .05$). However, group 1 was associated with more headache (18% of women) 3 hours after induction compared to group 2 (0% of women, $P = .038$).

Conclusion: IMN in addition to gemeprost is effective for second-trimester abortion, but is associated with more headache compared with gemeprost alone.

Second-trimester abortion for medical reasons is frequently performed by administration of prostaglandins or their analogs to soften the cervix uteri.[1-3] Gemeprost is the only prostaglandin currently licensed for cervical softening in the second trimester in Austria, Italy, and Germany; however, its use is associated with several adverse effects such as abdominal pain, nausea, vomiting, diarrhea, and vaginal bleeding.[4] The ideal agent for cervical softening should be clinically effective, with a low incidence of side effects, and easy to administer.

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Table I Baseline characteristics of women according to treatment allocation

	IMN + gemeprost (n = 38)	Placebo + gemeprost (n = 34)	*P* value
Age (y)	30.0 ± 6.1 (18-41)	29.8 ± 6.1 (19-41)	NS
Gestational age (wk)	17.7 ± 3.1 (12.4-23.3)	18.4 ± 3.3 (12.6-27)	NS
Indications for uterine evacuation			
Missed abortion	6 (15.8%)	6 (17.6%)	NS
Chromosomal abnormalities	11 (28.9%)	10 (29.4%)	
Anhydramnion	6 (15.8%)	1 (2.9%)	
Structural malformations	14 (36.8%)	17 (50%)	
Maternal causes	1 (2.6%)	0	
NOx serum levels (μmol/L)	13.7 ± 11.4	12.7 ± 9.0	NS

Results are shown as mean ± SD (95% CI shown in bracket) or as a number (%). *P* values were calculated with analysis of variance or χ^2 test.

Table II Characteristics of the abortion process and outcome of abortion in the IMN + gemeprost and the placebo + gemeprost group

Efficacy	IMN + gemeprost (n = 38)	Placebo + gemeprost (n = 34)	*P* value
Total patients allocated	40	40	
Patients excluded	2	6	
Patients analyzed for primary outcome	38 (100%)	34 (100%)	
Patients undergoing abortion within 48 h	33 (87%)	31 (91%)	
Patients not undergoing abortion within 48 h	5 (13%)	3 (9%)	
Induction-abortion interval (h)	23.2 ± 18.7	29.9 ± 31.7	.27

Results are shown as mean ± SD or as a number (%). The *P* value was calculated with analysis of variance.

Several lines of evidence indicate that nitric oxide (NO) is the ideal cervical softening agent. Administration of the NO donors isosorbide mononitrate (IMN), glyceryl trinitrate, as well as sodium nitroprusside to the posterior vaginal fornix were reported to reduce the cervical resistance before abortion in patients undergoing termination of pregnancy during the first trimester (12 weeks).[5,6] Pretreatment with 40 or 80 mg IMN to soften the cervix before first-trimester surgical termination of pregnancy resulted in a greater amount of symptom-free patients than gemeprost (60%-70% vs 14%, respectively; $P < .005$).[7]

NO donors have been shown to stimulate prostaglandin production in the human cervix after vaginal administration.[8,9] Even if NO did not stimulated prostaglandin production, the cervical softening effects of NO donors and prostaglandins would still be additive.[10] If this hypothesis is correct, this would allow the use of a lower number of interventions needed to affect cervical softening if a NO donor is given in combination with a prostaglandin compared with a prostaglandin given alone. In the current study we examined the effects of 40 mg of IMN administered intravaginally with gemeprost compared with gemeprost alone for second-trimester abortion. For that purpose, we had to consider carefully how often and in which dose IMN should be administered vaginally in combination with gemeprost. Gemeprost administered vaginally reaches maximum plasma levels after 2 to 3 hours, with detectable levels for at least 6 to 8 hours,[11] which justifies routine administration every 3 hours up to a maximum of 3 times a day.

Material and methods

This double-blind, randomized, placebo-controlled multicenter study was carried out at the Medical University of Vienna, Vienna, Austria, the University of Modena and Reggio Emilia, Modena, Italy, and the University of Jena, Jena, Germany. Before the initiation of the study, approval was granted by the human ethics committees of the 3 participating universities.

A total number of 80 white Austrian (n = 20), Italian (n = 40), and German (n = 20) women scheduled for second-trimester abortion were included in the study (Table I). Inclusion criteria were nulliparity, gestational age between 12 weeks + 0 days and 22 weeks + 6 days confirmed by transvaginal ultrasonography, singleton pregnancy, good general health, and age between 19 and 35 years. Exclusion criteria included cervicitis, vaginitis, diabetes mellitus, chronic obstructive pulmonal disease, simultaneous intake of anti-inflammatory drugs, or