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1 Effect of the addition of osmotic dilators to medical induction of
2 labor abortion: a before-and-after study.

3

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20

21 Abstract:

22

23 Objectives: The main objective of this study was to assess the induction-to-delivery
24 interval with or without the use of osmotic dilators for induced abortion. As secondary
25 objectives, women outcomes were assessed.

26 Study design: This retrospective single-center observational before and after study
27 reviewed records from a university hospital maternity unit from 2002 through 2016
28 and included all women undergoing abortion for medical reasons at and after 14
29 weeks of gestation. Two groups were compared: group “no dilators”, which used first
30 misoprostol without dilators, and group “dilators”, which used osmotic dilators before
31 misoprostol administration. The main outcome was the induction-to-delivery interval.

32 Results: The study included 491 women: 383 in group “no dilators” and 108 in group
33 “dilators”. The induction–delivery interval was significantly lower in the group
34 “dilators” compared to “no dilators” (427.7 min vs 639.7 min, $P<0.001$), as was the
35 cumulative misoprostol dose (990 μg vs 1449 μg , $P<0.001$). The delivery rate within
36 6 hours was significantly higher in the “dilators” group compared to “no dilators”
37 group (50.0% vs 29.8%, $P=0.002$).

38 Conclusion: The use of osmotic dilators for cervical ripening before administration of
39 misoprostol for induced abortion appears to be effective in reducing the induction-
40 delivery interval.

41

42 Keywords : induction of labor, delivery, osmotic dilators, misoprostol, abortion,
43 cervical ripening

44

45 **MAIN TEXT**

46

47 **Introduction**

48

49 In France, when a multidisciplinary medical committee has determined that incurable
50 fetal abnormalities or a serious threat to the mother's health exist, parents can
51 request a late abortion.[1] Two principal techniques are used for abortion.[2–5] The
52 first is dilatation and evacuation, using instruments. Some teams, especially in
53 English-speaking countries, use it as late as 24 weeks of gestation.[4,6] The second
54 technique is induction of labor and delivery, which is possible as early as 14 weeks
55 and thereafter, regardless of the term of the pregnancy.[3,7,8] This is the method
56 most frequently used in France.[9,10] There are currently no guidelines for the choice
57 of a method of induction for medical abortion. In this psychologically difficult context
58 for the couple, the ideal method should be as effective, rapid, and safe as possible.
59 Although the use of osmotic dilators for the cervical ripening needed for induction in
60 abortion has been reported, the value of this technique has not yet been
61 demonstrated.[3,7,11–13]

62 The main objective of this study was to assess the induction-to-delivery interval with
63 or without the use of osmotic dilators for induced abortion. As secondary objectives,
64 women outcomes were assessed.

65

66 **Material and methods**

67 In 2010, our obstetric department modified the protocol we use for induction of labor
68 for abortion. In the two groups, labor induction was preceded by orally administration
69 of mifepristone 200mg 36 hours before. Before 2010, labor was induced by the
70 administration of vaginal misoprostol alone; since then, osmotic dilators (Dilapan-S®)
71 are routinely used before misoprostol administration. The dose of vaginal misoprostol
72 was the same before and after 2010 and was 400µg every 3 hours for women with
73 no history of cesarean and reduced at 200 µg every 3 hours in case of history of
74 cesarean delivery. A feticide was performed for pregnancy over 22 gestational weeks
75 by cordonal injection of alfentanil (Rapifen®) 2mL follow by lidocaïne 2% 10 to 20mL.
76 Epidural analgesia was performed just before feticide and/or the first administration
77 of misoprostol. The cervix evaluation was performed systematically before dilators
78 placement. The osmotic dilators placement occurred in hospitalization, twelve hours
79 before the first dose of vaginal misoprostol, with administration of oral analgesics in
80 prevention of pain.

81 This single-center retrospective before-and-after study reviewed all cases of induced
82 abortion in our level 3 university hospital maternity ward between January 2002 and
83 June 2016. All women with singleton pregnancies who underwent induction of labor
84 for abortion after 14 weeks during the before and after study periods were included.
85 We then excluded women with a favorable cervix that enabled immediate amniotomy
86 (Bishop score ≥ 6) and those with a contraindication to the use of osmotic dilators
87 (signs of chorioamnionitis, rupture of the membranes). To limit the potential biases
88 associated with the change in protocol in 2010, deliveries during 2010 and 2011 were
89 also excluded.

90 Two groups were defined by the method of their induction, which differed by study
91 period: group 1, named “no dilators” group, included women with an abortion from
92 2002 through 2009, whose induction involved misoprostol alone; group 2, named
93 “dilators” group, included women with an abortion from 2012 through 2016, whose
94 labor was induced by osmotic dilators and then misoprostol. The principal endpoint
95 was the duration of labor, defined by the interval between the first administration of
96 misoprostol and delivery, expressed in minutes. The secondary outcome measures
97 were: the interval between the administration of misoprostol and the amniotomy, the
98 cumulative misoprostol dose, the rate of delivery within 24 hours, duration of
99 hospitalization, the correlation between the duration of labor and both fetal weight
100 and gestational age, and complications, such as failure of induction (defined by
101 failure of vaginal delivery), total or partial early placental retention (defined by the
102 total absence or incomplete placental delivery diagnosed by systematic ultrasound
103 exam), severe hemorrhage (defined by woman blood loss exceeding 1000 mL), or
104 infection (defined by the onset of pelvic pain associated with fever, laboratory-
105 confirmed inflammation, identification of the microorganism, or antibiotic therapy).
106 The other data collected concerned woman age, parity, uterine scars, number of
107 vaginal deliveries, gestational age at abortion, and obstetric condition (defined by the
108 Bishop score) at dilator placement or at first misoprostol for the group “no dilators”.

109 The first stage of the statistical analysis was a descriptive analysis of the indicators
110 collected, by calculations of the means, standard deviations, and range for the
111 continuous variables and of the percentages for the categorical variables. The
112 different outcome measures were compared by univariate analysis. Significance was
113 set at 5%. The quantitative variables were compared by Student's t test and the
114 qualitative variables by a Chi^2 or Fisher's exact test, as appropriate. A multivariate

115 analysis with a logistic regression model was performed to determine if the use of
116 dilators was an independent factor associated with a delivery within 24 hours after
117 labor induction. All confounding factors highlighted in the univariate analysis ($p < 0.1$)
118 were included in the logistic regression model. The Kaplan-Meier curves (induction-
119 delivery intervals) were compared by log-rank tests. Pearson's correlation coefficient
120 was used to assess the correlation between the duration of labor and both
121 gestational age and fetal weight. The analyses were performed with Stata software©
122 version 11, 2009 (Statacorp, College Station, TX).

123

124 The National Data Protection Authority approved this study (CNIL n° R2017-01) and
125 all women included gave their written consent.

126

127 **Results**

128

129 Between January 2002 and June 2016, abortion was performed after 14 weeks of
130 gestation for 706 women and was always medically indicated. After application of the
131 exclusion criteria, 383 women were included in the “no dilators” group and 108
132 women in the “dilators” group (Figure 1).

133

134 Table 1 summarizes the women's characteristics. The Bishop score was more
135 frequently 0 in the “dilators” group compared with the “no dilators” group (58.3% vs
136 46.7%, $P=0.02$). There was no significant difference in the distribution of the women
137 in the third trimester (≥ 28 weeks) (22.2 vs 29.8 %, $P=0.07$).

138

139 Women outcomes are reported in Table 2. The use of osmotic dilators (“dilators”
140 group) was associated with a significantly shorter induction-delivery interval (427.7
141 min vs 639.8 min, $P<0.001$), for a mean reduction of 33.2%. This reduction of
142 induction-delivery interval was significant between the two groups only before 28
143 gestational weeks and in case of unscarred uterus. The rates of deliveries within 6,
144 12, and 24 hours were all significantly higher in “dilators” group compared to “no
145 dilators” group (Figure 2). Half the women who had osmotic dilators placed have
146 delivered in the first 6 hours, compared with only 29.8% in the “no dilators” group
147 ($P<0.001$) and all women in “dilators” group have delivered in the 24 hours compared
148 to 95.6% in the “no dilators” group (Figure 2). After multivariate analysis, the use of
149 dilators was an independent factor associated with delivery in 24 hours after labor
150 induction (Odds ratio= 8.1 [2.3 – 28.9]).

151

152 There was significant difference regarding the rate of hemorrhage which is more
153 frequent in the “dilators” group. One case of failed induction and one of uterine
154 rupture were found in each group. One uterine rupture occurred in “no dilators”
155 group, in a woman with an unscarred uterus, and another in “dilators” group, in a
156 woman with two previous cesareans (Figure 2).

157

158 **Discussion**

159

160 In our study, the use of osmotic dilators appears to be an independent factor
161 associated with a shorter induction-delivery interval and with higher rates of delivery
162 within 24 hours. All women have delivered in 24 hours in the “dilators” group. The six
163 cases of infection were all observed in the “no dilators” group and could be explained
164 by their longer time in labor. We also found a higher rate of severe immediate
165 hemorrhages in the “dilators” group. Quantification of blood loss after vaginal
166 deliveries is difficult, and visual assessment of bleeding is known to underestimate it
167 substantially. Recent changes in practices include the use of graduated collection
168 bags and the weighing of used compresses. The difference observed here can
169 probably be explained by better quantification of blood loss during the second period
170 (“dilators” group).

171 The principal strength of our study is its before-and-after design, which enables us to
172 limit the biases due to the lack of randomization and to its retrospective nature, by
173 having only one factor vary between the groups: the use (or not) of osmotic dilators.
174 Moreover, our study has a large sample size; to our knowledge it is currently the only
175 study that combines so large a size with good control for potential bias. The
176 limitations of this study are associated with its single-center and retrospective nature
177 and with the absence of randomization.

178 Its results are consistent with those of Vincienne et al. and Chodankar et al., who
179 have reported that time to delivery is shorter for management by dilators+misoprostol
180 than for misoprostol only.[13,14] We have exactly the same results with Chodankar
181 et al. in terms of time to delivery and the difference is only the gestational age (13 to
182 24 weeks only) and the sample size which is more important in our study.[13] On the

183 other hand, our study differs from that of Vincienne et al. in two major ways that may
184 affect the result.[14] The first is that the misoprostol dose was different in the two
185 groups that they studied (200 micrograms every 3 hours regardless of gestational
186 age in the misoprostol-only group compared to 400 micrograms before 32 weeks and
187 50 micrograms after 32 weeks, every 3 hours in the dilators+misoprostol group). In
188 our study, besides the obstetric characteristics (Bishop score), only the absence of
189 osmotic dilators differentiates the two study groups; this makes it possible to study
190 the specific interest of their use. The second difference is the use of oxytocin to
191 replace misoprostol after amniotomy, while misoprostol administration continued until
192 delivery in our study. The passive and active phases of the first stage of labor that
193 take place in the delivery room are the longest stages and those the most at risk of
194 infectious and hemorrhagic complications.[7] The replacement of misoprostol by
195 oxytocin during labor can therefore influence the intervals studied. In our study, the
196 rate of women with an unfavorable Bishop score was higher during the second
197 period, a finding that further underlines the effect of osmotic dilators.

198 The global rate of complications found in our study is consistent with the results of
199 the literature. Nonetheless, because the onset of complications was relatively rare, it
200 is difficult to draw a definitive conclusion on this point because we cannot rule out the
201 possibility that our study lacked the power to show a difference.[11,15] We observed
202 one case of uterine rupture in each group, one of a woman with an unscarred uterus
203 and the other in a woman with two previous cesareans. It is difficult to attribute these
204 complications to the use of osmotic dilators. The uterine rupture rate observed in our
205 study (0.26% vs 0.93% respectively in the before and after groups) corresponds to
206 known risks of the induction of labor by prostaglandins, on the order of 1% among

207 women with no history of cesareans and up to 4.8% among women with previous
208 cesareans.[3,7,8,10–12,16–18]

209 Randomized, controlled comparative studies are necessary to confirm the interest of
210 osmotic dilators with misoprostol for induction of labor for women with medical
211 abortion. Such a multicenter study is currently underway in France, and we are one
212 of the participating centers. Results are expected in 2021 (NCT03194230).

213

214 **Conclusion**

215 The use of osmotic dilators with misoprostol, compared to misoprostol alone,
216 appears interesting for reducing the interval between induction of labor and delivery
217 in women undergoing medical abortion.

218

219 Author contributions: C.B., E.P.G. and O.M. designed the study; C.B., M.G.D. and
220 E.P.G. wrote the manuscript; M.G.D. , P.G. and M.D. collected and entered and the
221 data; O.M. and C.B. did the statistical analysis and all authors reviewed and
222 contributed to the manuscript.

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225 Conflicts of interest: none

226

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228

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288

289 **Figure Caption**

290 Figure 1: Flow Chart

291 Figure 2: Kaplan-Meier curves for the Misoprostol – Delivery Interval. *a. with or*
292 *without osmotic dilators. b. with or without osmotic dilators in women with no previous*
293 *cesarean delivery. c. with or without osmotic dilators in women with one or more*
294 *previous cesareans.*

295

296 **Tables**

297 Table 1: Characteristics of the populations in the two groups.

298

299 Table 2: Women outcomes

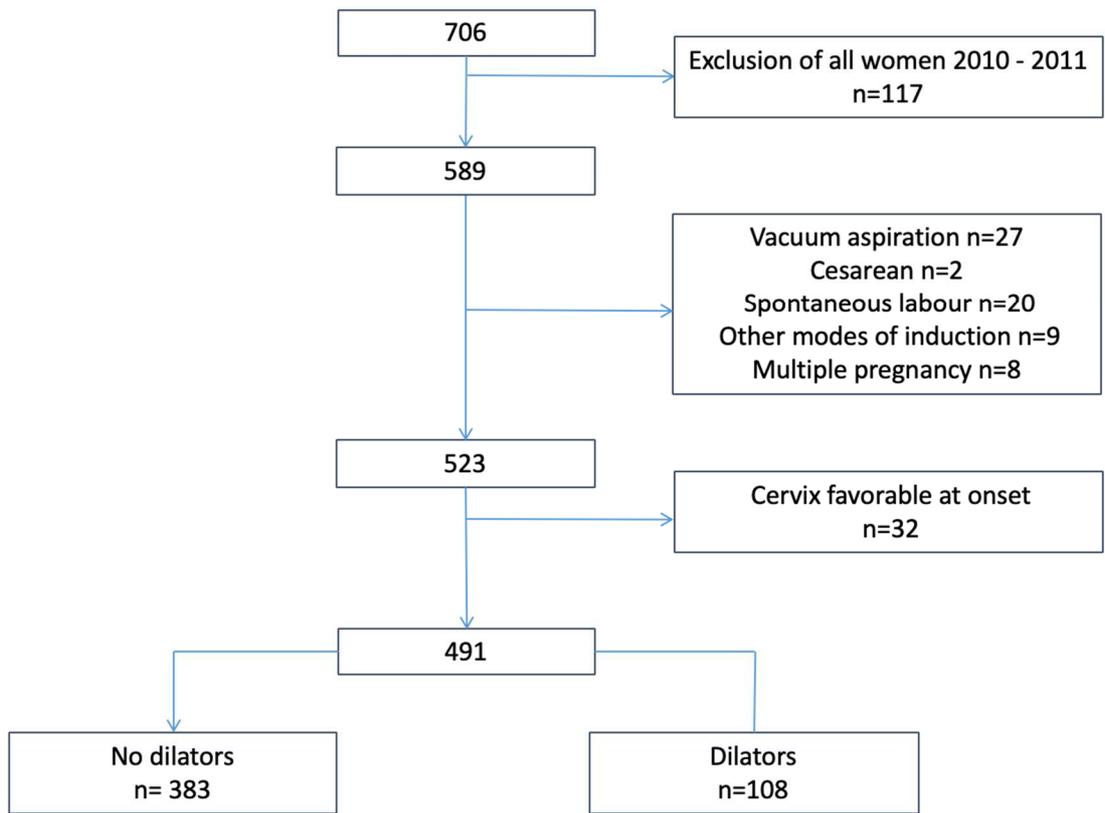
300

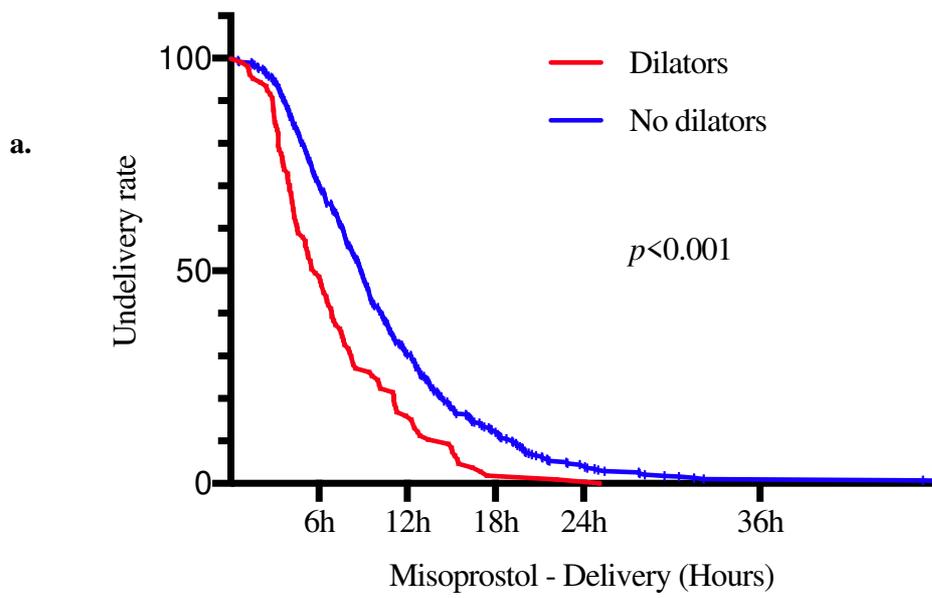
Identification

Selection

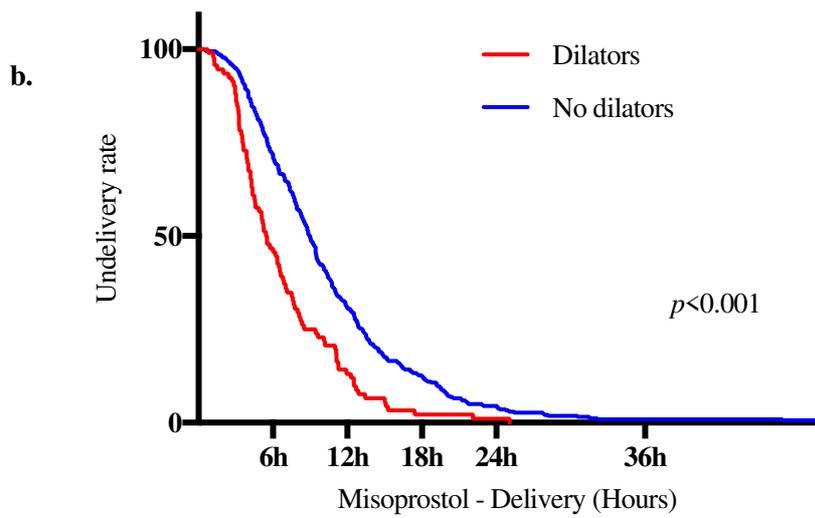
Eligibility

Inclusion





No history of cesarean



Previous cesarean

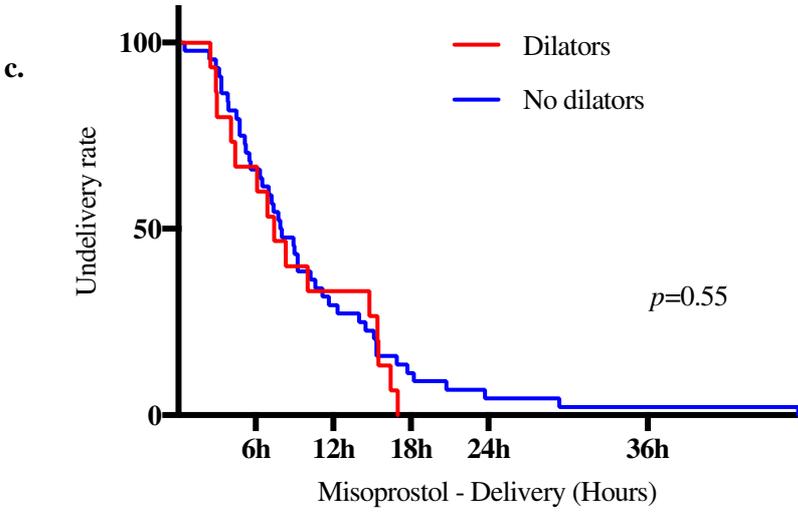


Table 1: Characteristics of the populations in the two groups.

	No dilators <i>n</i> = 383	Dilators <i>n</i> = 108	p
Age (years), <i>mean</i> ± <i>sd</i>	30.6 ± 6.1	30.4 ± 5.6	0.8
Nulliparity, <i>n</i> (%)	221 (57.7)	71 (65.7)	0.15
Previous cesarean, <i>n</i> (%)	44 (11.5)	16 (14.8)	0.41
Obesity, <i>n</i> (%)	33 (8.6)	21 (19.4)	0.03
Bishop score at 0, <i>n</i> (%)	179 (46.7)	63 (58.3)	0.02
Cephalic presentation, <i>n</i> / <i>N</i> (%)	113/242 (46.7)	27/60 (45.0)	0.48
Gestational age,			
- Median (range)	25 (14-39)	23 (14-37)	
- ≥ 28 weeks of gestation, <i>n</i> (%)	114 (29.8)	24 (22.2)	0.07

Table 2: Women outcomes

	No dilators <i>n</i> = 383	Dilators <i>n</i> = 108	p
Misoprostol - amniotomy interval (min), <i>mean</i> ± <i>sd</i>	333.6 ± 316	285.1 ± 239	0.15
Misoprostol – delivery interval (min), <i>mean</i> ± <i>sd</i>	639.7 ± 568	427.7 ± 280	<0.001
- ≥ 28 weeks of gestation (WG)	502 ± 321	482 ± 322	0.79
- < 28 WG	698.2 +/- 637	422 +/- 282	0.0001
- scarred uterus	657.6 ± 453.4	590 ± 376	0.70
- unscarred uterus	637.5 +/- 554.7	408.7 +/- 268.2	0.0001
Induction to delivery, n(%)			
- < 6 hours	114 (29.8%)	54 (50.0%)	0.002
- < 12 hours	265 (69.2%)	89 (82.4%)	0.002
- ≤ 24 hours	366 (95.6%)	108 (100%)	0.01
Cumulative misoprostol dose (µg), <i>mean</i> ± <i>sd</i> (<i>n</i> / <i>N</i>)	1449 ± 933	990 ± 759	<0.001
- unscarred uterus	1463 ± 663 (339/383)	995 ± 481 (92/108)	<0.001
- uterine scar	1336 ± 756 (44/383)	962 ± 653 (16/108)	0.25
Duration of hospitalization (days), <i>mean</i> ± <i>sd</i>	3.6 ± 1.5	3.6 ± 2.4	0.85
Maternal complications, <i>n</i> (%)			
- Placental retention	51 (13.3)	16 (14.8)	0.75
- Hemorrhage	5 (1.3)	10 (9.2)	0.002
- Infection	6 (1.6)	0	0.34
- Uterine rupture	1(0.3)	1 (0.9)	0.39