

# Use of Prostaglandins as Abortifacients

*Warren M. Hern*

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## PROSTAGLANDINS IN ABORTION

Since their introduction to clinical use in the early 1970s, no class of compounds has generated more research, controversy, and, perhaps, confusion than the prostaglandins. Naturally occurring prostaglandins were used successfully to terminate pregnancies in 1970 and 1971, and they were welcomed as "wonder drugs" in the abortion field. Physicians hoped that the prostaglandins would replace saline and other substances used for second-trimester abortion and result in lower complication rates.<sup>1</sup> Hypertonic saline solution given by intra-amniotic infusion was the most common method of second-trimester abortion in 1970.<sup>2</sup> But hypertonic saline was associated with serious and even fatal complications, such as hypernatremia, coagulopathy, hemorrhage, infection, and uterine injury.<sup>3,4</sup>

In fact, it appeared that prostaglandins had certain advantages over saline: the injection-to-abortion intervals were shorter, and the drugs could be used when saline was contraindicated.<sup>5</sup>

With experience, evidence has accumulated that, while highly useful in abortion practice, prostaglandins have important limitations. Some of these limitations have been modified by the introduction of synthetic prostaglandins and an increase in the variety of modes of application.<sup>5-8</sup>

## TYPES OF PROSTAGLANDINS

The "classic" prostaglandins include prostaglandin  $F_{2\alpha}$  ( $PGF_{2\alpha}$ ) and prostaglandin  $E_2$  ( $PGE_2$ ).<sup>9</sup> In recent years, these have been supplemented with, if not supplanted by, various ana-

logues with increasingly complex chemical structures.<sup>10,11</sup> These include the following:

- Prostaglandin  $E_1$  ( $PGE_1$ )
- 15(S), 15-methyl  $PGF_{2\alpha}$  (Prostin/15M)<sup>12,13</sup>
- 15(S), 15-methyl  $PGF_{2\alpha}$  methyl ester
- 15(S), 15-methyl  $PGE_2$
- 16-phenoxy w 17,18,19,20 tetranor  $PGE_2$  methyl sulfonylamide (sulprostone)<sup>14</sup>
- 9-deoxo-16,16-dimethyl-9-methylene  $PGE_2$
- 16,16-dimethyl-trans  $\Delta^2$   $PGE_1$  methyl ester (Gemeprost)

## MODES OF ADMINISTRATION

Early attempts to administer  $PGF_{2\alpha}$  intravenously resulted in abandonment of this method owing to severe gastrointestinal side-effects and pyrexia.<sup>15</sup> Subsequently, intra-amniotic infusion of the classic prostaglandins proved to be the most reliable route, since it resulted in low circulating levels of the drugs.

Efforts to produce materials or methods that could be self-administered or could be administered by persons with minimal skills resulted in the development of various prostaglandin analogues. The extraovular administration of  $PGF_{2\alpha}$ , for example, proved to be efficacious but associated with high complication rates.<sup>16</sup>

Intramuscular applications of the classic prostaglandins were too painful for consistent use, although the intramuscular use of some analogues is promising. In particular, the intramuscular use of Prostin/15M appears to be valuable in cases of late fetal death, fetal anomalies, ruptured membranes, and advanced pregnancies.<sup>17-23</sup>

The incorporation of prostaglandin analogues into suppositories and pessaries is one of the most promising modes of application. The disadvantage of temperature instability in earlier preparations is being overcome, although this remains a concern for use in developing countries.

## ADVANTAGES

### Extra-amniotic Administration (Classic Prostaglandins)<sup>24</sup>

The individual dose is low and well tolerated even if injected intravenously by mistake.

The total cumulative dose is low.

The frequency of prostaglandin-specific side-effects, such as vomiting and diarrhea, is lower than that following intra-amniotic administration of the same compound.

The procedure is suitable during the first weeks of the second trimester, when intra-amniotic administration is technically difficult.

### Intra-amniotic Administration (Classic Prostaglandins)

Hypernatremia is not a risk.

Inadvertent intravascular or intraperitoneal injection of PGF<sub>2α</sub> appears to be less dangerous (than saline), since PGF<sub>2α</sub> is rapidly metabolized.

There is less tissue damage from intramyometrial administration of PGF<sub>2α</sub>.

Consumptive coagulopathies appear to be less frequent with PGF<sub>2α</sub>.

### Intramuscular and Suppository Administration (Analogues)

Administration is easy.

Surgical skill is not required.

Suppositories may be self-administered.

Repeated doses are easily administered.

## CONTRAINDICATIONS

### Absolute<sup>25</sup>

Respiratory ailment (asthma, allergic bronchitis, emphysema, fibrocystic disease, bronchiectasis)

Sickle cell trait or anemia

Hydatidiform mole

Glaucoma<sup>26</sup>

Epilepsy<sup>26</sup>

Pulmonary hypertension<sup>26</sup>

### Relative<sup>27</sup>

Organic heart disease

Hypertension

Severe hypersensitivity (previous anaphylactic reaction)

Ulcerative colitis

Diabetes mellitus

Disorders of blood coagulation

Severe kidney disease

Severe liver disease

Any serious systemic disease

### Relative Contraindications to Transabdominal Intrauterine Administration

Previous abdominal surgery

Previous surgery on the uterus

Large uterine myomas or other pelvic tumors

Major congenital anomalies of the uterus

Rupture of the membranes

Failed saline induction

## COMPLICATIONS ASSOCIATED WITH PROSTAGLANDIN USE

High incidence of incomplete abortion<sup>28,29</sup>

High incidence of moderate to severe gastrointestinal symptoms, severe cramps, and pyrexia

High incidence of cervical and uterine trauma, including ruptured uterus and uterovaginal fistulas<sup>30</sup>

High incidence (as much as 7%) of signs of life in the fetus on expulsion<sup>31</sup>

## DISADVANTAGES

High cost of materials

Possibility of serious fetal deformity if abortion attempt fails<sup>32</sup>

Higher complication rates than other methods of abortion<sup>33-37</sup>

Bygdeman adds several disadvantages for first-trimester pretreatment;<sup>24</sup> these are long pretreatment time, uterine pain, and gastrointestinal side-effects.

## SURVEY OF PROSTAGLANDIN LITERATURE

A bewildering thicket of medical literature confronts the clinician who seeks to evaluate the

desirability of prostaglandins for use in abortion. There are numerous attempts to compare the various prostaglandin preparations with each other according to various modes of administration, usually in second-trimester abortion.<sup>26,38-49</sup> Prostaglandins in second-trimester abortion are compared with other preparations and methods such as urea amnioinfusion,<sup>50,51</sup> saline amnioinfusion,<sup>35-37,52-54</sup> and dilatation and evacuation (D&E).<sup>33-35</sup> Prostaglandins are used with saline,<sup>55</sup> rivanol,<sup>56</sup> and urea,<sup>52,57</sup> and prostaglandins alone and in combination with other materials are used with laminaria preparation of the cervix.<sup>58-61</sup>

In first-trimester abortion, there have been attempts to use prostaglandin suppositories as the principal method of abortion, self-administered or otherwise, with mediocre results.<sup>62-66</sup> The high rate of incomplete abortions and side-effects associated with the use of prostaglandin suppositories in first-trimester abortion compares unfavorably with vacuum aspiration.<sup>62-64,66,67</sup> Brenner and co-workers, for example, found at least a 35% failure rate for patients receiving prostaglandin analogues for first-trimester abortion.<sup>67</sup> For this reason, it is unlikely that the suppositories will supplant vacuum aspiration or D&E abortion in the future.

Prostaglandin suppositories, however, may prove to be useful in cervical softening when applied a few hours before the anticipated surgical procedure. Numerous studies have used prostaglandin suppositories to soften the cervix prior to first-trimester abortion.<sup>60,68-81</sup> While some studies have shown this procedure to be effective, there is little evidence that prostaglandins offer any advantage over hygroscopic dilators such as laminaria or Lamicel.<sup>68,72,82,83</sup> Sidhu and Kent found a 50% reduction in blood loss in first-trimester abortion following the use of prostaglandin E analogue suppositories.<sup>84</sup> Vacuum aspiration procedures under general anesthesia resulted in a mean blood loss of 69 ml for study patients versus 151 ml for control patients.

With minimal complication rates in first-trimester vacuum aspiration abortion under local anesthesia so heavily documented, it is difficult to see the justification for studies with high complication rates in order to test prostaglandin products. A case in point is a report by Amarin and Grant in which first-trimester patients were subjected to indwelling intrauterine catheters through which a prostaglandin preparation was periodically infused over 24 hours.<sup>85</sup> Part of the study was to determine whether inexperienced operators could perform abortions in this manner. An exceedingly high proportion of patients in one group (39.4%) experi-

enced serious complications. The high infection rate was reduced by the use of prophylactic metronidazole.

Complication rates, including blood loss and infection as well as catastrophic results such as uterine rupture, have tended to be high with prostaglandin preparations of all kinds,<sup>14,16,28,29,38,86</sup> even in the hands of experienced physicians. Complications such as severe gastrointestinal disturbances experienced by 33% to 100% of all prostaglandin patients are universally reported as "side-effects."<sup>38</sup>

The most disturbing aspects of prostaglandin use, aside from a high proportion of live births in second-trimester abortion, have been the numerous reports of catastrophic occurrences such as sudden cardiovascular collapse and uterine rupture.<sup>28,30,87-98</sup> It is true that the risk of uterine rupture may be reduced by avoidance of oxytocic drugs,<sup>99</sup> but it appears that some patients may be at unpredictable risk of lethal complications from prostaglandins in abortion.

These risks, as well as the risks of other complications, have led to spirited debate concerning the relative safety of prostaglandins compared with other methods of abortion. Two sets of authors may arrive at diametrically opposed conclusions concerning the same subject.<sup>37,54</sup> Bygdeman, reporting a 3% transfusion rate for prostaglandin patients versus 0.8% for saline patients and a 2.8% rate of uterine injury for prostaglandin patients (4.4% for primigravidas), concludes that prostaglandins are safer than saline for second-trimester abortions.<sup>54</sup> Bygdeman does not include D&E as a method for second-trimester abortion. Grimes and Cates, however, cite higher complication rates to conclude that saline is safer than prostaglandins, adding that the rate of live birth following abortion is five to 40 times higher with prostaglandins than with saline.<sup>37</sup>

Increasingly, D&E abortion has supplanted other methods of abortion in the second trimester in the United States. Comparisons between D&E and prostaglandins have repeatedly shown prostaglandin use to have higher complication rates than D&E.<sup>33-35</sup> Grimes and co-workers, for example, found that prostaglandin patients were 5.7 times as likely to experience a complication as D&E patients.<sup>34</sup> Robins and Surrago found a 50% higher transfusion rate for prostaglandin patients.<sup>33</sup> Nearly a third of the prostaglandin patients experienced pyrexia, and similar proportions experienced gastrointestinal side-effects. Duenhoejter and Gant found that 42.6% of 122 prostaglandin patients had complications.<sup>28</sup> Of 600

prostaglandin patients, Anderson and Steege had follow-up data on only 14%, but at least 2.6% of all patients underwent blood transfusions, and 13% were judged to have experienced "excessive" blood loss.<sup>29</sup> Citing a wide variety of studies including the Joint Program for the Study of Abortion (JPSA), Grimes and Cates concluded that D&E is two to three times safer in terms of complication rates and death-to-case rates than either saline or prostaglandin procedures.<sup>100</sup> While complication rates are frequently not provided in clinical reports of prostaglandin studies, conservative estimates of major complication rates of 2.5% to 5% must inevitably be compared with major complication rates of 0.3% or less in large D&E series.<sup>101-104</sup>

Death-to-case rates have been higher for prostaglandin than for D&E, although the trend is reversed in the latest collection of 1981 statistics published in late 1985 by the Centers for Disease Control (CDC).<sup>105</sup> The small numbers of deaths recorded, changes in CDC data collection efforts, and long delay in release of the CDC data make interpretation of the mortality statistics difficult.

In at least one study, patients experiencing D&E procedures reported less psychological trauma than patients experiencing prostaglandin induction.<sup>106</sup>

Part of the problem in evaluating different second-trimester abortion methods is that combination methods are now being used in clinical practice. These innovations make it difficult to draw straight-line comparisons. Also, small numbers (especially in numbers of deaths), varying methodologies in clinical practice, reporting errors, and varying methods of analysis make it difficult to determine the procedure of choice. Serious methodological flaws reduce the value of most published clinical reports. These flaws make it almost impossible to draw firm conclusions from the results of clinical studies.

Overall, the clinician must be guided in choosing a treatment regimen that minimizes risks for patients according to the best evidence available.

## CONCLUSION

A review of the extensive literature concerning prostaglandins shows that a variety of preparations are available and give varying results according to the authors' experience and interpretation of data. It is clear from existing evidence that prostaglandins will not supplant vacuum aspiration for first-trimester abortions.<sup>63</sup> There are no significant advantages, and complications and

side-effects are numerous. Prostaglandins may have a role in softening the cervix prior to first-trimester abortion, but there are no convincing evidence that prostaglandins are superior to hygroscopic dilators for this purpose.

In early second-trimester abortion, D&E is far safer than prostaglandins or any combination of prostaglandins with other materials. In late second-trimester abortion, it appears that prostaglandins may provide supplemental effect when used with other primary methods such as urea or saline, but all methods must be measured against accumulating experience with the low complication rates obtainable by D&E. Another factor to consider is that there are no absolute contraindications to D&E abortion.

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