Intraamniotic Prostaglandin $F_{2\alpha}$ Dose–Twenty-Four-Hour Abortifacient Response

W. E. BRENNER[A], C. H. HENDRICKS, J. I. FISHBURNE, Jr., L. STAUROVSKY, J. BRAAKSMA, and R. TAFT

Abstract □ Prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) was administered intraamniotically to 132 midtrimester gravidas by one of six dose schedules to determine the dose–24-hr. abortifacient response. Single doses between 15 and 50 mg. and multiple doses between 15 and 25 mg. were administered to three groups each, the latter regimen at 6-hr. intervals. Dose–response relationships with both the single- and multiple-injection methods were different in patients of different parities and gestational ages. Interpretation of the dose–response relationships indicated that: (*a*) no one-dose schedule will obtain maximum rates of abortion in all types of patients; (*b*) single injections of greater than 50 mg. of $PGF_{2\alpha}$ are indicated in multiparas of greater than 16 weeks' gestational age, (*c*) in patients at 16 weeks' gestation or less, the low dose multiple-injection schedule attains high abortion rates that probably cannot be achieved by higher multiple-injection methods or any single-injection method; (*d*) it is unlikely that any significant increase in effectiveness can be obtained by multiple injections in excess of 25 mg. initially and repeating an identical dose in 6 hr. in patients greater than 16 weeks' gestation; and (*e*) it is unlikely that any increase in effectiveness will result from single doses in excess of 25 mg. in multiparas of 16 weeks' gestation or less. Complications were not of such severity or frequency as to limit the practicability of these schedules.

Keyphrases □ Prostaglandin $F_{2\alpha}$—intraamniotic dose–24-hr. abortifacient response □ Intraamniotic prostaglandin $F_{2\alpha}$ administration—dose–24-hr. abortifacient response □ Abortion—24-hr. response after intraamniotic prostaglandin $F_{2\alpha}$ administration □ Dose–response relationships—prostaglandin $F_{2\alpha}$ intraamniotic administration and 24-hr. abortifacient response

Although the intraamniotic administration of prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) has been demonstrated to be an effective means of aborting pregnancies after 14 weeks' gestation (1, 2), the dose schedule safely resulting in the greatest frequency of abortion within the shortest period of time remains to be demonstrated. In an effort to make the search for this dose less arduous for both the subjects and investigators, the dose–24-hr. abortifacient response relationships were studied.

MATERIALS AND METHODS

One hundred thirty-two physically healthy gravidas between 10 and 23 menstrual weeks' gestation received $PGF_{2\alpha}$ intraamniotically by one of six dose schedules to induce therapeutic abortion[1]. There were no significant differences in the compared characteristics between the groups (Table I).

Prostaglandin $F_{2\alpha}$ in a concentration of 5 mg./ml. of diluent was injected through a polyethylene catheter[2] inserted into the amniotic cavity *via* an 18-gauge, thin-wall needle by either the transabdominal or transvaginal approach. The initial 5 mg. $PGF_{2\alpha}$ was injected over 5-min., while the remainder of the dose was injected over the following 5-min. period.

One of six $PGF_{2\alpha}$ dose schedules was used. The single-dose schedules were:

Group I (15 mg.)—Twenty gravidas were injected with 15 mg.

Group II (25 mg.)—Thirty-one gravidas were injected with 25 mg.

Group III (50 mg.)—Twenty-four gravidas were injected with 50 mg. at the initiation of the study, with no further $PGF_{2\alpha}$.

The multiple-dose schedules were:

Group IV (15–15 mg.)—Ten gravidas were injected with 15 mg. at the initiation of the study and an identical dose 6 hr. later.

Group V (25–25 mg.)—Twenty-two gravidas were injected with 25 mg. at the initiation of the study and an identical dose 6 hr. later if abortion had not occurred.

Group VI (25–25–25 mg.)—Twenty-five gravidas were injected with 25 mg. at the initiation of the study with an identical dose 6 and 12 hr. later if abortion had not occurred.

For this study, all trials were declared a failure if abortion (either complete or incomplete) did not occur within 24 hr. of the initial injection. Abortion was classified complete when both the fetus and placenta were completely expelled from the uterus; it was considered incomplete when the placenta was not completely expelled from the uterus. Abortion interval was the period of time from the initial injection to expulsion of the fetus from the uterus. Gestational age was calculated as the nearest number of whole weeks from the first day of the patient's last normal menstrual period. A subject was classified as multiparous if she had one previous delivery after 20 weeks of gestation. Differences at the $p < 0.05$ level were considered statistically significant.

RESULTS

Single-Dose Schedules—Although there was an increase in effectiveness when the dose was raised from 15 mg. (Group I) to 25 mg. (Group II), there was an insignificant increase when the dose was raised from 25 to 50 mg. (Group III) (Fig. 1 and Table II). Increases in frequency of abortion (9%) and in the mean abortion time (3.1 hr.) and differences in the rates of incomplete abortions noted when the dose was raised from 25 to 50 mg. were statistically insignificant.

Different dose–response relationships were noted for patients of different parities and gestational ages (Fig. 2). As the dose was progressively increased in nulliparous patients, increasing rates of abortion were observed. In contrast, as the dose was progressively increased in multiparous patients, decreasing rates of abortion were observed.

Differences were also observed between patients of greater than 16 weeks' gestation (>16 weeks) and 16 weeks' gestation or less (≤16 weeks). In gravidas >16 weeks' gestation, significantly higher rates of abortion were observed with each increase in dose. Higher

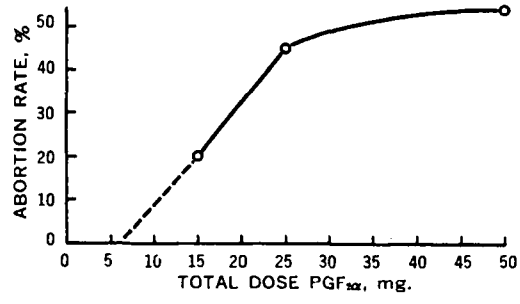

Figure 1—*The 24-hr. abortion rate in percent with three single-injection dose schedules of intraamniotic prostaglandin $F_{2\alpha}$ detailed in the text. The dashed line is extrapolated as the best fitting line between existing frequencies.*

[1] At the Clinical Research Unit of the North Carolina Memorial Hospital, University of North Carolina.
[2] VX020, Becton Dickinson and Co., Rutherford, N. J.

Table I—Characteristics of 132 Gravidas Treated by One of Six Intraamniotic Prostaglandin $F_{2\alpha}$ Dose Schedules

	Group					
	I	II	III	IV	V	VI
	Dose Abbreviation					
	15 mg.	25 mg.	50 mg.	15–15 mg.	25–25 mg.	25–25–25 mg.
Patients, number	20	31	24	10	22	25
Race, number						
Negroid	6	14	5	6	11	13
Caucasian	14	17	18	4	11	12
Mongoloid	0	0	1	0	0	0
Parity, number						
Nulliparas	12	19	17	6	13	16
Multiparas	8	12	7	4	9	9
Gestation, weeks						
Mean	16.8	16.9	16.5	16.5	16.1	16.0
(Range)	(14–20)	(14–21)	(12–23)	(14–20)	(10–23)	(14–20)
≤16 Weeks, number	9	16	13	5	15	16
>16 Weeks, number	11	15	11	5	7	9
Marital status, number						
Single	16	21	21	7	15	21
Married	4	10	3	3	7	4
Weight, kg.						
Mean	51.7	61.0	57.8	54.0	63.2	64.9
(Range)	(44–79)	(48–80)	(45–90)	(43–107)	(41–102)	(48–118)
Height, in.						
Mean	64.6	64.0	64.0	63.7	63.3	65.0
(Range)	(52–70)	(59–69)	(59–71)	(58–68)	(59–67)	(60–72)

abortion rates were not obtained with single injections in excess of 25 mg. in patients ≤16 weeks' gestation. In nulliparous patients and in patients >16 weeks' gestation, the abortifacient response was higher when the dose was increased from 25 to 50 mg. In patients ≤16 weeks' gestation, the 50-mg. dose was no more effective than the 25-mg. dose, and in multiparas the 50-mg. dose was less effective.

Multiple-Dose Schedules—Although the overall results indicated no increase in the frequency of abortion within the 24-hr. period for dosage levels higher than 15 mg. repeated in 6 hr. (Group IV) (Fig. 3), differences in abortion rates were noted for patients of different parities and gestational ages (Fig. 4). Nulliparas and patients ≤16 weeks' gestation had significantly lower rates of abortion when the dose was increased above that of Group IV. However, in multiparas and patients ≤16 weeks' gestation, higher rates of abortion were noted to the Group V level (25 mg. repeated in 6 hr.). Although the mean abortion time of Group V was shorter and the rates of incomplete abortion were higher for Group VI, these differences were not statistically significant.

Single-Dose Compared to Multiple-Dose Schedules—All multiple-dose schedules resulted in higher abortion rates than the single-dose schedules (Fig. 5). The multiple-injection schedule of Group VI, however, did not result in a statistically significant increase over the single injection of 50 mg. (Group III).

When the differences in dose schedules were analyzed for patients of different parities and gestational ages (Fig. 6), the multiple-injection schedules were as effective, if not more effective, in comparable total doses. In both nulliparas and patients ≤16 weeks' gestation, the Group IV dose schedule was the most effective. In contrast, in multiparas and patients >16 weeks' gestation, the Group V (25–25 mg.) schedule was the most effective. Single doses of 50 mg. (Group III) appeared equally as effective as the 50-mg. dose administered in two separate 25-mg. doses (Group V) in nulliparas and patients >16 weeks' gestation.

Complications—Although the minor complications were frequent, no serious complications were observed (Table III). The frequency

Table II—Twenty-Four-Hour Abortion Results of 132 Gravidas Treated by One of Six Intraamniotic Prostaglandin $F_{2\alpha}$ Dose Schedules

	Group					
	I	II	III	IV	V	VI
	Dose Abbreviation					
	15 mg.	25 mg.	50 mg.	15–15 mg.	25–25 mg.	25–25–25 mg.
Patients, number	20	31	24	10	22	25
Abortions, number (%)	4 (20)	14 (45)	13 (54)	7 (70)	15 (68)	15 (60)
Complete	2 (10)	9 (29)	6 (25)	6 (60)	14 (63)	10 (40)
Incomplete	2 (10)	5 (16)	7 (29)	1 (10)	1 (05)	5 (20)
Mean time, hr.	19.0	14.5	17.6	17.4	13.8	15.2
(Range)	(15.6–21.5)	(4.8–21.0)	(8.5–23.9)	(8.5–23.0)	(6.5–23.8)	(4.0–22.5)
Nulliparas, number	12	19	17	6	13	16
Abortions, number (%)	0 (0)	7 (37)	11 (65)	5 (83)	9 (69)	9 (56)
Complete	0 (0)	6 (32)	4 (24)	5 (83)	9 (69)	8 (50)
Incomplete	0 (0)	1 (05)	7 (41)	0 (0)	0 (0)	1 (6)
Multiparas, number	8	12	7	4	9	9
Abortions, number (%)	4 (50)	7 (58)	2 (29)	2 (50)	6 (67)	6 (67)
Complete	2 (25)	3 (25)	2 (29)	0 (0)	5 (56)	2 (22)
Incomplete	2 (25)	4 (33)	0 (0)	2 (50)	1 (11)	4 (44)
≤16 Weeks' gestation						
Patients, number	9	16	13	5	15	16
Abortions, number (%)	2 (22)	6 (38)	5 (38)	5 (100)	10 (67)	9 (56)
Complete	1 (11)	4 (25)	2 (15)	4 (80)	10 (67)	7 (44)
Incomplete	1 (11)	2 (13)	3 (23)	1 (20)	0 (0)	2 (12)
>16 Weeks' gestation						
Patients, number	11	15	11	5	7	9
Abortions, number (%)	2 (18)	8 (53)	8 (73)	2 (40)	5 (71)	6 (67)
Complete	1 (9)	5 (33)	4 (36)	1 (20)	4 (57)	3 (33)
Incomplete	1 (9)	3 (20)	4 (36)	1 (20)	1 (14)	3 (33)

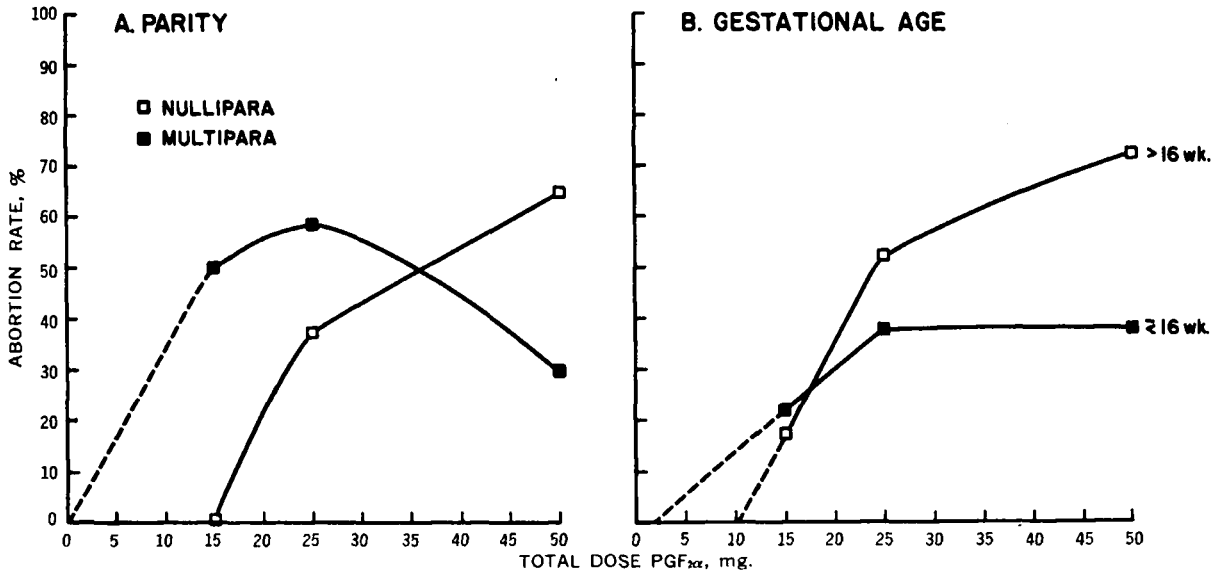

Figure 2—*The 24-hr. abortion rate in percent with three single intraamniotic prostaglandin $F_{2\alpha}$ dose schedules (detailed in the text) for: A, nulliparas and multiparas; and B, patients 16 weeks' gestation or less (≤16 wk.) and patients greater than 16 weeks (>16 wk.). The dashed line is extrapolated as the best fitting line between existing points.*

of complications did not appear to correlate with dose, parity, or gestational age.

DISCUSSION

In an effort to develop practicable methods of midtrimester abortion, investigators have pursued both multiple- and single-intraamniotic $PGF_{2\alpha}$ injection techniques (3–7). If intraamniotic injection is as effective as intravenous infusion, high abortion rates within 24 hr. are possible (8). Search for the most effective dose schedules has been conducted by administering progressively increasing amounts in an increasing number of injections. Results from these studies indicate that more than 50% of the patients can be aborted without serious complications within 24 hr. by a variety of unaugmented $PGF_{2\alpha}$ dose schedules. Initially, only small groups of patients were necessary to demonstrate differences in effectiveness between these schedules because there were large differences in the rates of abortion. However, single- and multiple-injection dose schedules with smaller differences in rates of abortion have been developed which require large numbers of patients to demonstrate differences with any statistical certainty. Therefore, the progressively-increasing-the-dose method is no longer a practical means for determining the dose schedule with the highest rates of abortion and tolerable side effects.

Because most therapeutic agents have certain characteristics in common, by determining one of these characteristics, the dose–response relationship, one should be able to use it to make the search for the most effective dose schedule less arduous for patients and investigators. Although dose–response relationships are constant for a drug under identical conditions (9), in this study the midtrimester patients differ from each other in many variables, some of which greatly influence the dose–response relationships. Two of these variables are parity and gestational age.

Single-Injection Techniques—Although doses of greater than 25 mg. of $PGF_{2\alpha}$ do not appear warranted from the results in the whole group (Fig. 1), parity and gestational age are important variables in

Table III—Complications in 132 Gravidas Treated by One of Six Intraamniotic Prostaglandin $F_{2\alpha}$ Dose Schedules

	Group					
	I	II	III	IV	V	VI
	Drug Abbreviation					
	15 mg.	25 mg.	50 mg.	15–15 mg.	25–25 mg.	25–25–25 mg.
Patients, number	20	31	24	10	22	25
Vomiting						
Patients, number (%)	8 (40)	8 (26)	15 (62)	7 (70)	10 (45)	14 (56)
Mean number episodes	1.6	0.7	1.3	1.1	1.0	1.0
(Range)	(0–4)	(0–8)	(0–5)	(0–3)	(0–5)	(0–4)
Antiemetics						
Patients, number (%)	2 (10)	5 (16)	2 (8)	1 (10)	3 (14)	5 (20)
(Range)	(0–3)	(0–2)	(0–2)	(0–1)	(0–1)	(0–3)
Pain						
Patients, number (%)	14 (70)	11 (35)	23 (96)	7 (70)	16 (73)	19 (76)
Mean doses meperidine	1.6	0.8	2.8	1.5	1.2	1.8
(Range)	(0–5)	(0–4)	(0–9)	(0–6)	(0–4)	(0–6)
Diarrhea						
Patients, number (%)	0 (0)	1 (3)	6 (25)	2 (20)	1 (5)	0 (0)
Fever >100°F						
Patients, number (%)	1 (5)	1 (3)	3 (13)	0 (0)	1 (5)	6 (24)
≤16 Weeks' gestation, number	9	16	13	5	15	16
Vomiting, number (%)	4 (44)	4 (25)	7 (54)	4 (80)	7 (47)	9 (56)
>16 Weeks' gestation, number	11	15	11	5	7	9
Vomiting, number (%)	4 (36)	4 (27)	8 (73)	3 (60)	3 (43)	5 (56)
Nullipara, number	12	19	17	6	13	16
Vomiting, number (%)	5 (42)	5 (26)	13 (76)	5 (83)	7 (54)	10 (62)
Multipara, number	8	12	7	4	9	9
Vomiting, number (%)	3 (38)	3 (25)	2 (29)	2 (50)	3 (33)	4 (44)

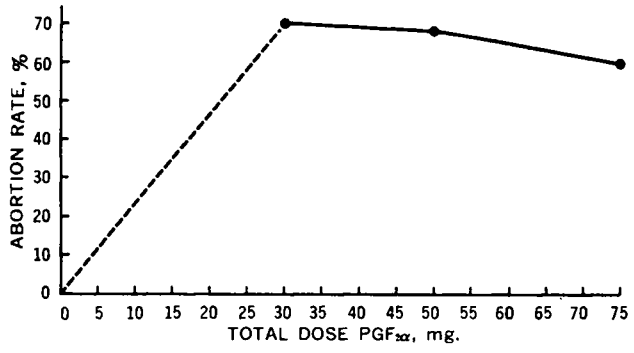

Figure 3—*The 24-hr. abortion rate in percent with three intraamniotic prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) multiple-injection dose schedules (detailed in the text). The dashed line is an extrapolation to zero abortion rate at zero dose of $PGF_{2\alpha}$.*

significant variable, two conclusions appear justified: (*a*) doses greater than 15 mg. initially with an identical dose repeated 6 hr. later probably will not increase the 24-hr. abortion rate in nulliparas ≤16 weeks' gestation, and (*b*) doses greater than 25 mg. repeated in 6 hr. will probably not improve the 24-hr. abortion rate in multiparas ≤16 weeks' gestation.

Comparison of Single- and Multiple-Dose Schedules—Overall, these multiple-dose schedules achieved higher 24-hr. abortion rates than the single-injection schedules (Fig. 5). However, when parity and gestational age were considered, the single-dose abortifacient response curves had not reached a plateau (no further increase in frequency of abortion with further increase in dose) at the 50-mg. (Group III) dose in nulliparas and patients >16 weeks' gestation. Rates in multiparas receiving a single injection of 25 mg. (Group II) were not significantly different from those in multiparas receiving multiple injections of 25 mg. (Groups V and VI), and rates greater than about 65% probably cannot be achieved for all multiparas with either type of dose schedule. The multiple-injection technique appears definitely superior for patients ≤16 weeks' gestation. Although the single-dose schedule curve reached a plateau after 25 mg. for these patients at less than a 50% abortion rate, the multiple-injection schedule used in Group IV (15–15 mg.) resulted in a 100% abortion rate. Whether the dose–response curve for single doses higher than 50 mg. in nulliparas and patients >16 weeks' gestation will reach a plateau or surpass the rates achieved with multiple injections remains to be demonstrated. Finally, it does not appear that any one dose, whether it is administered by single-injection or multiple-injection methods, will be maximally effective in patients of all gestational ages and parities.

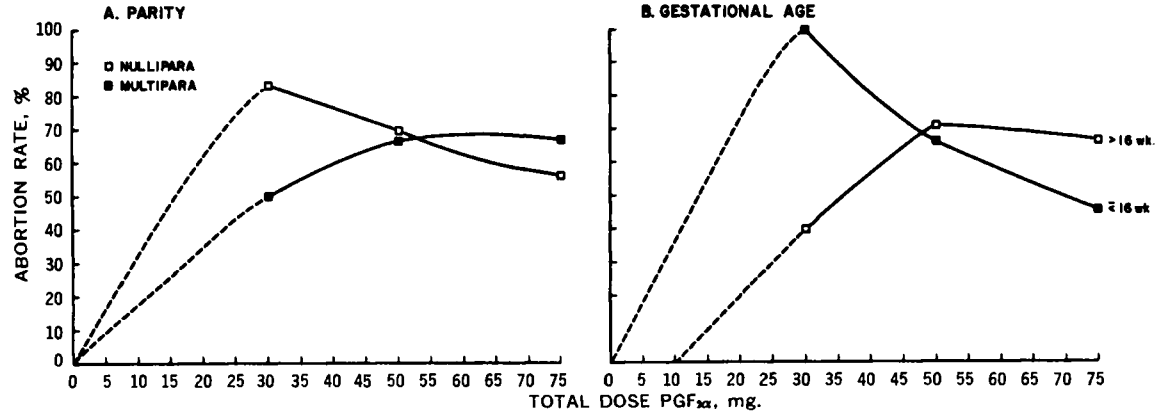

Figure 4—*The 24-hr. abortion rate in percent with three multiple intraamniotic prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) dose schedules (detailed in the text) for: A, nulliparas and multiparas; and B, patients 16 weeks' gestation or less (≤16 wk.) and patients greater than 16 weeks' gestation (>16 wk.). The dashed line is the extrapolation of either the best fitting line between existing points or to zero abortion rate at zero dose of $PGF_{2\alpha}$.*

the dose–response relationship (Fig. 2). Two conclusions appear warranted as a means of increasing the 24-hr. abortifacient efficiency: (*a*) doses in excess of 25 mg. in multiparas ≤16 weeks' gestation probably will not increase the rate, and (*b*) investigation of single injections greater than 50 mg. in nulliparas >16 weeks' gestation may improve the rate.

Multiple-Injection Schedules—Within the limits of these dose schedules, it appears from the overall results that there is no benefit to increasing the dose schedule above an initial injection of 15 mg. and repeating an identical dose in 6 hr. However, parity and gestational age are significant variables (Fig. 4). Interpretation of multiple-injection dose–response relationships is even more limited than that of single-dose schedules because of the many dose combinations possible. Although there were not enough patients in this series to determine whether parity or gestational age was the more

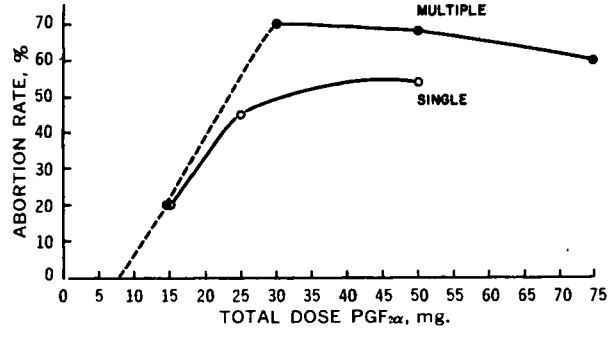

Figure 5—*The 24-hr. abortion rate in percent for three single and three multiple intraamniotic prostaglandin $F_{2\alpha}$ dose schedules (detailed in the text). The dashed lines are extrapolations.*

Complications—Because the dose schedules investigated were not associated with any serious complications and minor complications were of minimal severity, the effective schedules can be used clinically. Chlorpromazine and diphenoxylate hydrochloride/atropine sulfate[3] were demonstrated to be effective in decreasing the frequency and severity of vomiting and diarrhea, respectively (1, 10). One can only speculate upon whether premedicating patients to prevent minor complications will be advisable with the most effective dose schedule when it is identified.

Even though one can make certain hypotheses from dose–response curves, comparative series of different dose schedules will be necessary to verify these hypotheses. Dose–response relationships are absolutely reproducible only when all conditions are equal —a situation unimaginable in clinical medicine. However, once the significant variables are identified, the dose–response relationships are within ranges useful for clinical purposes. Two variables significantly modifying the dose–response relationship have been identified: parity and gestational age. As the information expands, the relative importance of these and other conditions should be specified.

[3] Lomotil, Searle. (Each tablet contains 2.5 mg. diphenoxylate hydrochloride and 0.025 mg. atropine sulfate.)

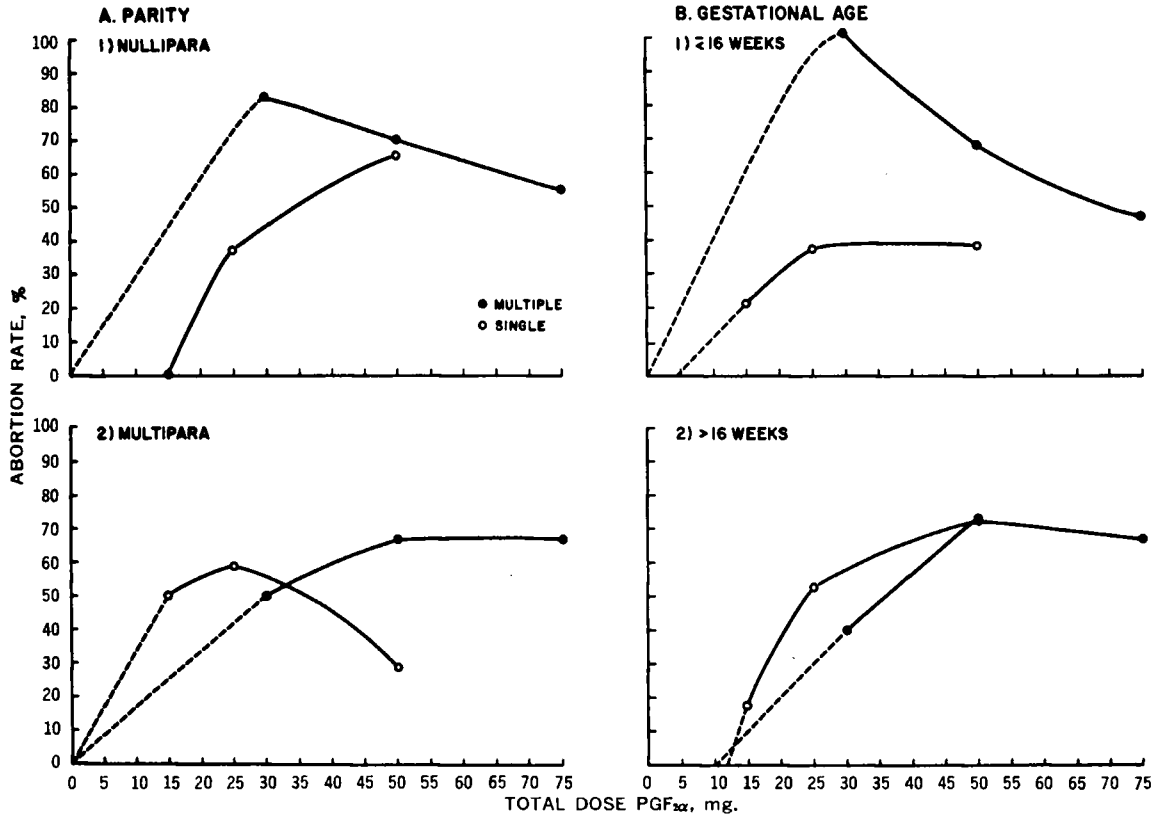

Figure 6—*The 24-hr. abortion rates in percent with three single- and three multiple-dose intraamniotic prostaglandin $F_{2\alpha}$ schedules (detailed in the text) for: A, patients of different parities (nulliparas and multiparas); and B, patients of different gestational ages [16 weeks' gestation or less (≤16) and greater than 16 weeks' gestation (>16)]. The dashed lines are extrapolations.*

Interpretation of the dose-response relationships indicates that further study of the following is desirable to improve the abortion rates: (*a*) single doses greater than 50 mg. in nulliparas and patients >16 weeks' gestation, (*b*) single doses in the range of 25 mg. in multiparas and patients <16 weeks' gestation, (*c*) multiple doses in the range of 15 mg. repeated in 6 hr. for nulliparas and patients >16 weeks' gestation, and (*d*) multiple doses in the range of 25 mg. repeated in 6 hr. for multiparas and patients >16 weeks' gestation. Although these interpretations of the dose-response relationships appear to be logical, extensive clinical trials will be necessary to confirm these hypotheses.

REFERENCES

(1) W. Brenner, C. H. Hendricks, J. T. Braaksma, J. I. Fishburne, Jr., F. G. Kroncke, Jr., and L. G. Staurovsky, *Amer. J. Obstet. Gynecol.*, **114**, 511(1972).

(2) W. E. Brenner, C. H. Hendricks, J. T. Braaksma, and J. I. Fishburne, Jr., in "Prostaglandins in Fertility Control," Third Conference on Prostaglandins in Fertility Control, S. Bergstrom, K. Green, and B. Samuelsson, Eds., Stockholm, Sweden, 1972, pp. 139–155.

(3) W. E. Brenner, C. H. Hendricks, J. T. Braaksma, J. I. Fishburne, Jr., and L. G. Staurovsky, *J. Reprod. Med.*, **9**, 456(1972).

(4) M. Bygdeman, F. Beguin, M. Toppozada, and N. Wiqvist, in "Prostaglandins in Fertility Control," Third Conference on Prostaglandins in Fertility Control, S. Bergstrom, K. Green, and B. Samuelsson, Eds., Stockholm, Sweden, 1972, pp. 129–136.

(5) C. A. Ballard and E. J. Quilligan, *J. Reprod. Med.*, **9**, 397 (1972).

(6) P. G. Gillett, R. A. H. Kinch, L. S. Wolfe, and C. Pace-Asciak, *ibid.*, **9**, 416(1972).

(7) G. G. Anderson, J. C. Hobbins, V. Rajkovic, L. Speroff, and B. V. Caldwell, *Prostaglandins*, **1**, 147(1972).

(8) W. E. Brenner, *Amer. J. Obstet. Gynecol.*, **113**, 1037(1972).

(9) "The Pharmacological Basis of Therapeutics," 4th ed., L. S. Goodman and A. Gilman, Eds., Macmillan, New York, N. Y., 1970, p. 20.

(10) A. C. Wentz, K. Austin, and T. M. King, *Amer. J. Obstet. Gynecol.*, **115**, 27(1973).

ACKNOWLEDGMENTS AND ADDRESSES

Received November 10, 1972, from the *Department of Obstetrics and Gynecology, University of North Carolina, Chapel Hill, NC 27514*

Accepted for publication January 16, 1973.

Presented at APhA Academy of Pharmaceutical Sciences, 13th national meeting, Chicago, Ill., November 5–9, 1972.

Supported in part by grants from the National Institute of Child Health and Human Development (HD-04148-03), the General Research Centers, the Program of the Division of Research Sources, the National Institutes of Health (RR-46), and the International Fertility Research Program of the Carolina Population Center of the University of North Carolina (AID/csd 2979). The Upjohn Co. supplied prostaglandin and financial assistance.

▲ To whom inquiries should be directed.