

Figure 7. The effect of prostaglandins on the fecal blood loss during indomethacin administration.

Dr Marc Bygdeman had just started his thesis work with Dr von Euler when the pure prostaglandins became available. He studied the effects of the different prostaglandins first *in vitro* and then *in vivo* in Dr Ulf Borell's Department at the Karolinska together with Dr Nils Wiquist. They first demonstrated clinically that PGE<sub>1</sub> causes uterine contractions when injected in small amounts. This of course led to the expectation that administration of prostaglandins might initiate labor or cause pregnancy interruption (63-65).

Dr Sultan Karim was the first to report on the clinical use of prostaglandins to initiate labor.

The first therapeutic abortion with PGF<sub>2α</sub> was done in May 1969 at the Karolinska Institute. During the remainder of the year the scientists at the Karolinska and also Drs Karim and Filshie in Uganda conducted further studies with PGF<sub>2α</sub> and PGE<sub>2</sub>. The results of both groups were published in the same number of *Lancet* in January 1970 (66, 67).

An intense activity then started all around the world exploring these findings with normal prostaglandins and later with some of the analogues as shown in Fig. 4.

## APPROXIMATE DOSES FOR PREGNANCY INTERRUPTION







	PGF <sub>2α</sub>	PGE <sub>2</sub>	15(S) 15 Me F <sub>2α</sub>	16,16 diMe E <sub>2</sub>
INTRA VENOUS 	~ 100 mg (50-100 µg/min)	~ 5 mg 5 µg/min	~ 5 mg 5 µg/min	~ 0.5 mg 0.5 µg/min
INTRA AMNIOTIC 	40-50 mg (1×)	5-10 mg (1×)	2.5 mg (1×)	
EXTRA AMNIOTIC 	~ 5 mg (~ 9×0.75 mg)	1-2 mg (6×)	1 mg (1×)	
I. VAGINAL SUPPOSITORIES 	[ 250 mg (5 × 50 mg)]	60-80 mg (3-4 × 20 mg)	~3 mg (Me-ester) (1 × 3 mg)	~4 mg (4 × 1 mg)
I. MUSCULAR 	—	—	2 mg (6 × 0.3)	
ORAL 	—	—	—	0.2-0.6 mg (60% Success)

Figure 8. Summary of early clinical trials indicating approximate doses for interruption of pregnancy.

The early clinical data that were obtained in Stockholm are summarized in Fig. 8 (66-73).

The two natural prostaglandins PGE<sub>2</sub> and F<sub>2α</sub> were first studied extensively. When they were administered i. v. they caused very pronounced side effect. When administered intraamniotically or extraamniotically the side effects were tolerable.

The 15(S)15-methyl PGF<sub>2α</sub> that was supplied by the Upjohn Co., was then studied and found to be much more active and giving much less side effects. It could also be injected i. m., and we developed vaginal suppositories containing the methyl ester. It is now a registered drug in many countries.

16,16-dimethyl PGE<sub>2</sub> was even more active-sometimes also very effective after oral administration of less than a milligramme. It caused, however, more side effects and furthermore had stability problems. Recently an analogue of 16,16-dimethyl PGE<sub>2</sub> in which the carbonyl group at C9 has been replaced by a methylene group is being extensively studied as it combines high activity with stability and very low side effects (74).

At that time an important development was initiated by SIDA (the Swedish International Development Authority). In the sixties they had become heavily involved in supporting family planning in many developing countries. However, they found that the methods available left much to be desired and therefore were considering how best to stimulate and support research and development in the field.

The Director, Mr Ernst Michanek and Mr Carl Wahren had developed

advanced plans to start an international research foundation located here at the Karolinska for this purpose. However, for various reasons, it was decided to make a feasibility study of an alternative arrangement together with the Ford Foundation and WHO, in which I had the honor to participate. This resulted in the creation of WHO's "Special programme" for research on human reproduction in 1971-72. The work should be focused on the needs of developing countries. The voluntary contributions to the programme soon exceeded ten million US dollars annually of which more than half were provided from Swedish sources during the seventies.

One of the "Task Forces" of the programme was devoted to exploring the potential of the prostaglandins to interrupt pregnancy. During the first live years I had the stimulating assignment as chairman of this group of outstanding experts. The exploratory work done at the Karolinska and by Dr Karim's group formed the basis for large international coordinated clinical trials. Figure 9 indicates the locations of the cooperating clinics and Fig. 10 the number of cases completed. The Task Force has continued its activities under the chairmanship of Dr Bygdeman.

The most important new development has been the interruption of pregnancy during the "postconceptional" period, i.e. the first three weeks after a missed menstrual period.

I have a very vivid memory of a late evening in Bombay when Dr Borell, Dr Bygdeman and myself were compiling results of abortions during different weeks of pregnancy and found a success rate of practically 100 per cent complete abortions during this period (Fig. 11). This observation has been studied extensively, and Dr Bygdeman et al. has just completed a successful trial with a hundred cases in Stockholm in which the patients even administered the drug themselves in their home. This method obviously has a very great potential especially in developing countries.

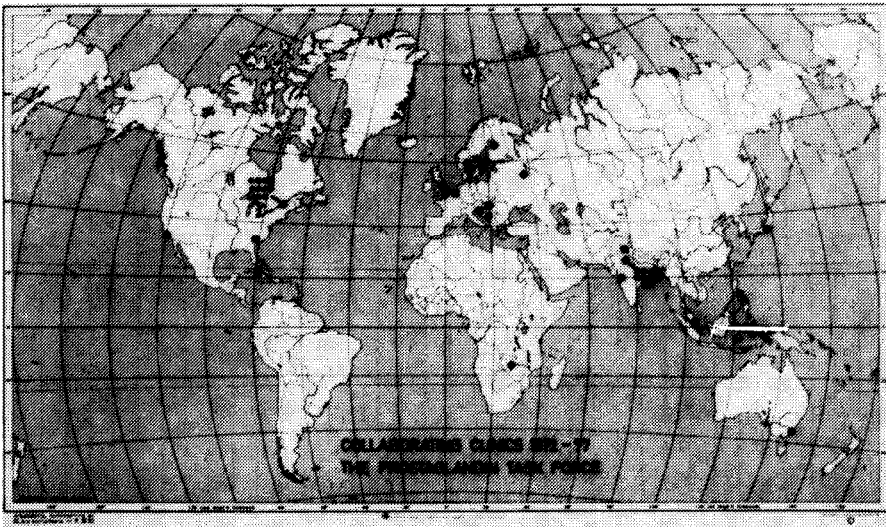


Figure 9. Participating clinics in coordinated trials of the WHO Prostaglandin Task Force.

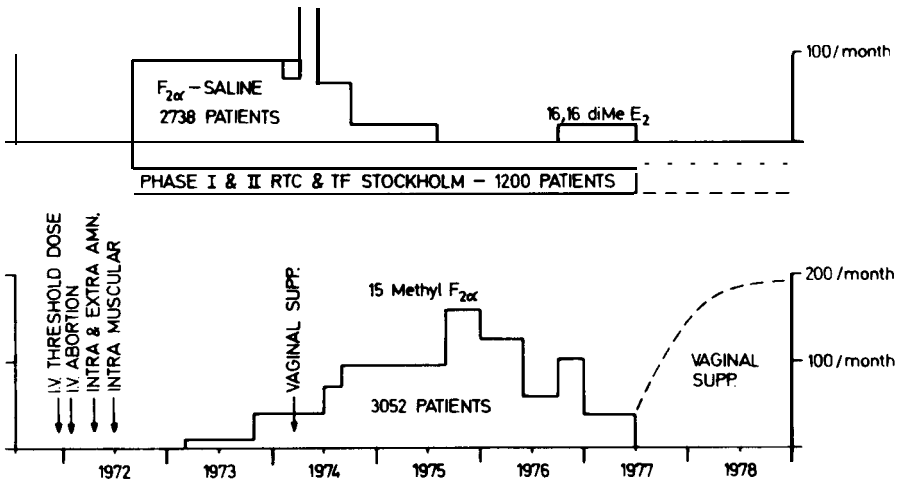


Figure 10. Number of patients participating in coordinated trials of the WHO Prostaglandin Task Force.

USE OF PROSTAGLANDINS FOR INTERRUPTION OF PREGNANCY

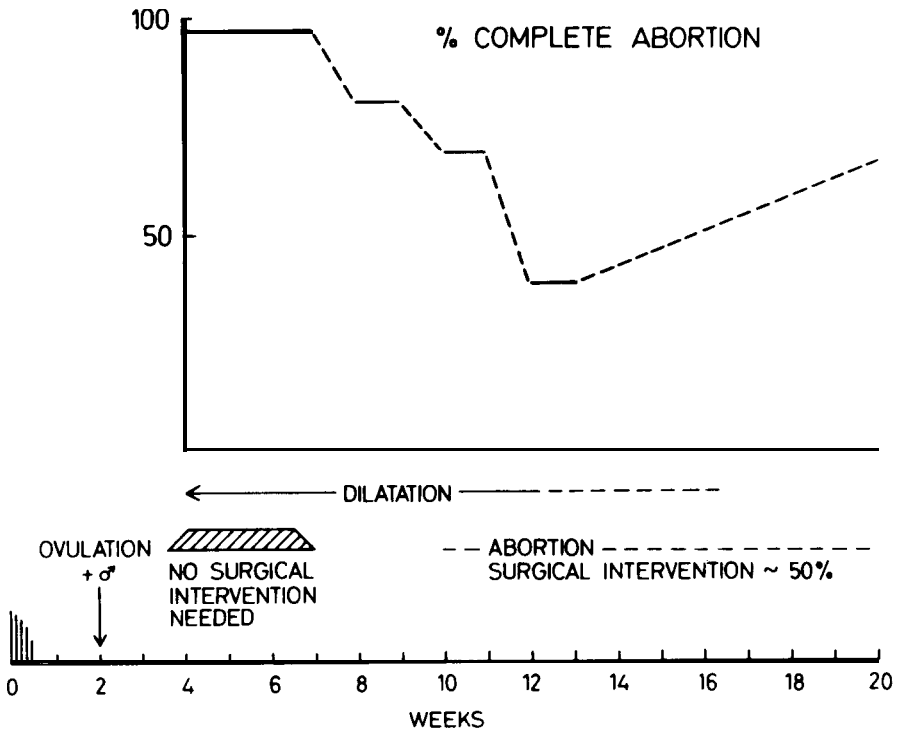


Figure 11. Per cent of "complete" abortions after interruption with prostaglandins during different weeks of pregnancy.

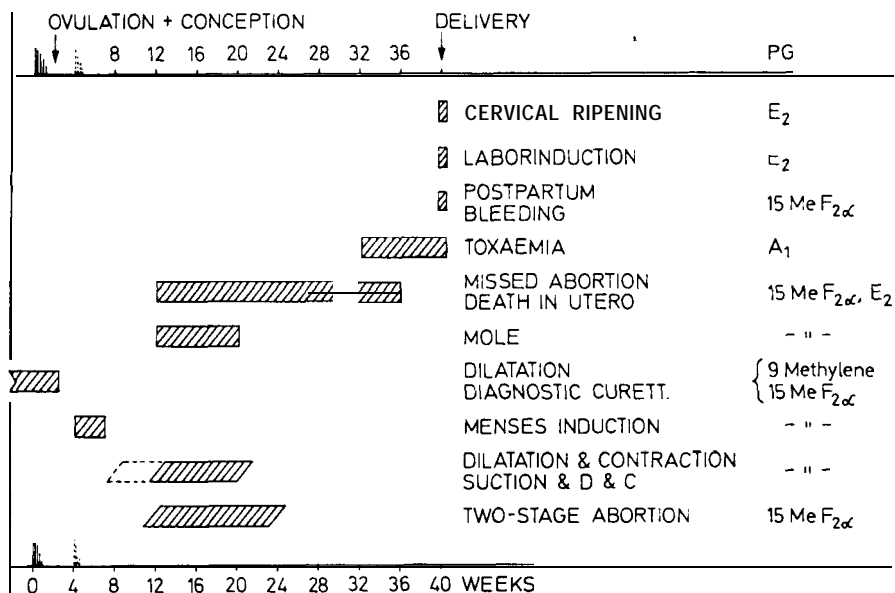


Figure 12. Summary of therapeutic utility of prostaglandins in human fertility

The therapeutic use of prostaglandins is, however, not limited to interruption of pregnancy. It is being used for labor induction, treatment of serious bleeding after delivery and dilatation for diagnostic curettage. Promising results have been reported of treating eclampsia with  $\text{PGA}_1$ , by Dr M. Topozada in Alexandria.

A summary of the use of prostaglandins in the fertility area is given in Fig. 12.

Prostaglandins have also found extensive use in animal husbandry especially for "synchronization" of herds of cattle, i.e. after injection of cows with 25 mg of  $\text{PGF}_{2\alpha}$  at an appropriate time, their cycles are interrupted and the whole herd can be inseminated three days later.

My presentation has of necessity been very short and sketchy and will be complemented by my colleagues.

The prostaglandin precursors and the enzymic systems appear to be present in practically all nucleated animal cells. They can biosynthesize characteristic mixtures depending on cell type and conditions on appropriate stimulation. As the highest concentration is found in the lowest animal species one can speculate that the ease of autoxidation of the precursor acids - a reaction that has even been reported to produce prostaglandins in minute amounts (75) - has led to their utilization in metabolism early on in development and for many different functions.

They are apparently mainly playing a role as local regulators even if  $\text{PGF}_{2\alpha}$  functions as a classical hormone in sheep, where it is produced in the uterus at the end of the cycle and transported in the blood to the ovary where it causes luteolysis.

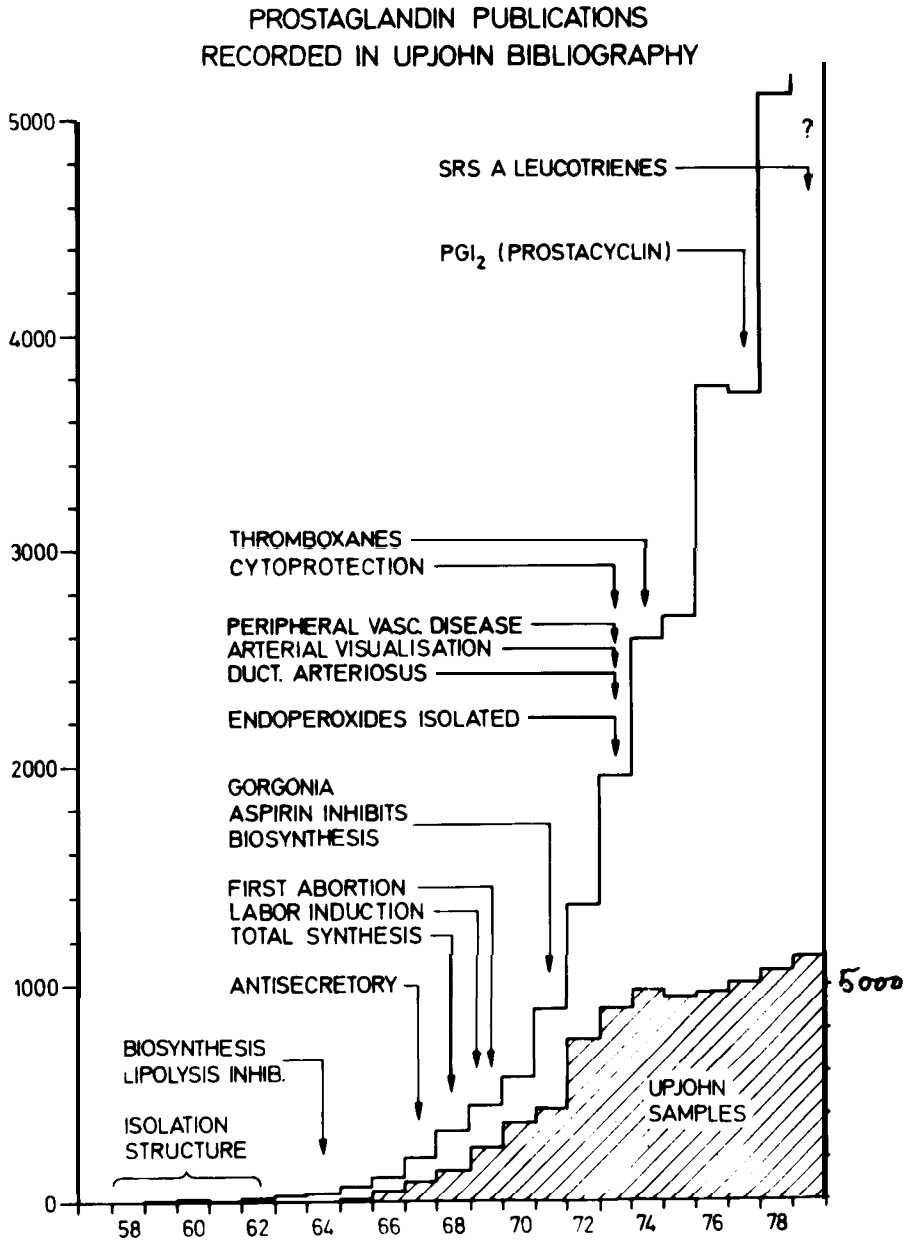


Figure 13. Annual publications related to prostaglandins in relation to the scientific development of the field. Free samples of prostaglandins distributed by the Upjohn Co., Kalamazoo.

The complex pattern of the arachidonic acid metabolism makes studies of the roles of prostaglandins in the complex regulatory mechanisms in organs like the kidney, lung etc. a difficult and challenging task.

Figure 13 illustrates how the field has developed from the early publications on the isolation, structure and biosynthesis to the present level of more than live thousand papers annually.

'How did all these scientists get their prostaglandins?' It is illustrated in Fig. 13. The Upjohn Company has sent out something like 75000 free samples during this period, and you can see that there is a correlation between the number of publications and samples up to about 1970. At that point the prostaglandin containing coral was found in the Mexican Gulf. A number of pharmaceutical industries collected corals, started synthetic programmes and then also supplied samples to scientists.

At this moment it is appropriate to point out that the whole prostaglandin field had been very much slower in developing without the outstanding research and development work and generous supply policy that was initiated and organized at the Upjohn Co. by Dr David Weisblat.

The prostaglandin story again illustrates the importance of interaction between the pharmaceutical industry and the academic biomedical scientists. In this case the special programme for human reproduction of the World Health Organization has also greatly contributed to the speed of development and to the buildup of research and development capabilities in this field in developing countries.

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