

Thiersch J B. Therapeutic abortions with a folic acid antagonist, 4-aminopteroylglutamic acid (4-amino P.G.A.) administered by the oral route. *Amer. J. Obstet. Gynecol.* 63:1298-304, 1952.
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4-Aminopteroylglutamic acid (4-amino PGA) given in nontoxic doses to pregnant women induced malformation and death in the fetuses. With that, an entire new field was opened mandating investigation of all drugs given to pregnant women for their teratogenic effect on the fetus. A second specific effect was noted on the reduction of production of chorionic gonadotropins. [The *SCI*® indicates that this paper has been cited in over 205 publications since 1955.]

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"It all started in 1948 at the Sloan-Kettering Institute in New York, while I was studying the toxicity of folic acid antagonists. A bitch, treated with a nontoxic dose of 4-aminopteroylglutamic acid (4-amino PGA), bled vaginally and aborted. The animal was not supposed to have been pregnant. I took this single observation seriously and followed it up with a number of experiments in mice, rats, and dogs studying the effects of folic acid antagonists in pregnant animals and fetuses. From this evolved the fact of a differential toxic-

ity of drugs between mother and fetus with a teratogenic effect of the drugs in different stages of pregnancy. In the course of the study, it soon became evident that the idea to control reproduction of the pregnant female with antimetabolites was accompanied with the danger of malformation in surviving fetuses. The whole approach was therefore abandoned. However, the fact remains that the compounds given to human mothers might induce malformation in the offspring. This was demonstrated ten years later when, with thalidomide, the human experiments preceded the animal work and large numbers of malformations were induced in the human fetus.

"Subsequently, the teratogenic effects of drugs on the fetus led to legislation in the US in 1962 demanding careful evaluation of drug effects on the fetus before a compound is recommended for use in pregnant women. The striking inhibitory effects on the production of chorionic gonadotropins led to the introduction of folic acid antagonists into the therapy of chorionic carcinoma.

"The effect of 4-amino PGA in pregnant women and its teratogenic action on the human fetus was the forerunner of many other compounds coming out of the field of chemotherapy of cancer.^{1,2}

"I believe this publication is so highly cited because it opened up a new field—the effect of drugs on the fetus *in utero*."

1. Thiersch J B. Control of reproduction in rats with the aid of antimetabolites and early experiences with antimetabolites as abortifacient agents in man. *Acta Endocrinol.* (Suppl. 28):37-45, 1956.

2. Effects of antimetabolites on the fetus and litter of the rat *in utero* (second report).

International Conference on Planned Parenthood, 6th. India. 1959. Report of the proceedings: family planning: motivations and methods. London: International Planned Parenthood Federation, 1959. p. 154-64.