

TABLE 2.
Total cycles of clinical experience with ENOVID.
(as of May 1964)

CLINICAL GROUP	CYCLES OF USE
Wiseman ⁸	6,299
Binks, Cambourn, and Papworth ⁹	843
Wisdom ¹⁰	3,967
Chinnatamby ¹¹	3,453
Satterthwaite	
Humacao ¹²	1,525
Comparative ¹³	2,443
Tyler ¹⁴	2,092
García and Pincus ¹⁵	6,138
Flowers ¹⁶	2,975
Burket ¹⁷	1,841
Andrews and Andrews ¹⁸	521
Mears ¹⁹	181
Mears ²⁰	1,288
	<u>33,506</u>

metriosis treated daily with 12 to 28 times the norethynodrel dose contained in ENOVID-E.

These massive doses were given every day—not cyclically—for nine to twelve months. After this treatment, the women whose courses were followed either by measurement of basal body temperature or by endometrial biopsy gave evidence of spontaneous ovulation within six to eight weeks.

It is generally accepted that ENOVID-E and ENOVID inhibit ovulation by reducing pituitary gonadotropin secretion. The prompt resumption of ovulation when medication is suspended indicates that gonadotropin inhibition is entirely reversible—that prolonged administration of ENOVID-E or ENOVID has no discernible effect on post-treatment pituitary function. There is no contrary evidence. There are no reports of any serious toxic manifestations involving the pituitary or any other endocrine organ as a result of ENOVID or ENOVID-E administration. Again, observations during and after cyclic use of these agents are supported by experience with the continuous administration of high doses in patients

with endometriosis. In these women, too, there is an apparent resumption of normal gonadotropin function³¹ after ENOVID therapy.

Commenting on long-term inhibition of the anterior pituitary, Parkes³⁶ reminds us that “the ovulation-producing activity of the human pituitary gland is inhibited for a year or more during pregnancy and lactation; so in this respect the continued use of the pill may be likened to a rapid succession of pregnancies. However undesirable in other ways, a succession of pregnancies is not usually regarded as . . . endocrinologically catastrophic.”

Ovarian biopsies revealed no deleterious effects after prolonged cyclic administration of higher doses than those received by women taking ENOVID-E. Actual counts were made of the number of primordial follicles in the ovaries of ENOVID-treated women and normal, untreated women. Among the women in the study⁵ were some who had received ENOVID for as long as twenty cycles. García and Pincus²⁵ consider these follicle counts “reassuring in that the follicle population density is not significantly different from the normal control counts for the respective age groups.”

Cytologic studies of the vagina and endometrial biopsies have also revealed³² no harmful effects after larger contraceptive doses than those afforded by ENOVID-E. Once more, the confirmatory findings in women treated for endometriosis are particularly interesting; endometrial biopsies and subsequent pregnancies in these women offer no evidence³¹ that the endometrium has been functionally compromised by high doses of ENOVID administered daily for months.

In reviewing the responses to prolonged ENOVID-E or ENOVID therapy, Pincus²¹ reported: “No significant change in the incidence of irregularities of the breasts, abdomen, fundus, vaults and adnexae, introitus, or in the proportion of palpable ovaries occurs either in relation to the duration of medication or in comparison with control subjects.”

The suggestion that oral contraceptives may delay the menopause has been dismissed by Flowers³⁷ with the comment that “we have not found the fountain of youth.” There is no evidence that the suspension of ovulation during frequent