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DO PROGESTINS REGULATE MENSTRUAL CYCLES?

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What is the medical evidence that progestins can "regulate" menstrual cycles? The inference has been that by using a prescribed regimen of treatment, irregular menstruators will miraculously menstruate every 28 days thereafter. The whole idea has been misconstrued by the general public and the common belief is that the moral licitness of the use of progestins to regulate menses means taking them indefinitely. An even more ridiculous misconception by some is shown by the patient who comes to the gynecologist and says that her confessor has "granted her permission" to use the progestins for a period of 2 years in order to regulate her menses. It is of course, not known if this is the advice of a misinformed priest, or the interpretation the penitent wished to put upon a priest's advice. Be that as it may, the object of this paper is not to condemn, but to emphasize the fact that there is a very widespread and absurd confusion existing among priests, patients and physicians. The second object is to examine the medical evidence upon which any such medical and theological opinion was based.

First of all, it is going to be difficult for us to agree about who is an irregular menstruator. Most gynecologists' experience is that every woman has cycles that vary from 25 to 35 days and that such variation should not even be considered unusual. Furthermore, it is a fact that every woman does vary this much and if she denies it, it is only because she has not been an accurate observer or kept accurate records. When records are kept, as was shown in one recent large and statistically significant series¹ only 15% of the time did menstruation fall on the 28th day of the cycle. Those who would argue that it is normal to menstruate every 28 days and that it is within the bounds of good treatment to say that every woman does menstruate every 28 days need to heed this significant fact.

Very often the woman who confronts the gynecologist with a plea for a prescription for progestins to regulate her will answer, when asked, that she is so irregular that she is unable to use rhythm, that her cycles vary from 27 to 32 days. This borders on the ridiculous, to be called irregular. Be that as it may, it is true that there are variants of the physiological who are going to have cycles longer than 35 days. For the sake of eliminating argument and in the interest of evaluating our subject, let us arbitrarily then set the upper limit of normal as 40 days.

¹Marshall, John, *The Infertile Period*, Helicon Press, 1964

Having agreed then that cycles that last longer than 40 days represent abnormality, let us try to categorize it diagnostically. We might refer to this condition as oligomenorrhea or secondary amenorrhea. Oligomenorrhea is the same as "spasmodic" secondary amenorrhea. Therefore, the difference between oligomenorrhea and secondary amenorrhea is semantic.

Before the confusion wrought by the progestins, gynecologists were not inclined to treat such states of secondary amenorrhea. In treating this subject, Brown and Kistner² once summed up the general gynecologic opinion by saying:

Secondly, in the absence of proved organic lesions, amenorrhea as a clinical symptom warrants treatment only as it relates to disturbed emotional states or to infertility.

Perhaps the woman who considers this irregularity a hazard to her practice of rhythm has a disturbed emotional state, but this is not likely to have been what these authors meant.

Let us not even argue the point as to whether such treatment of secondary amenorrhea is warranted. Let us assume that it is; then what is the medical evidence that progestins will treat it satisfactorily? If we turn to the literature of the G. D. Searle Company, manufacturers of Enovid³ we find the following:

²Brown & Kistner, *Essential of Human Reproduction*, Oxford Press, New York, 1958, p. 155

³G. D. Searle & Co., *Physicians' Product Brochure No. 67*, Chicago 80, Illinois, 1963

Kupperman and Epstein³⁸, Roland, Smith and Romney¹², Roland³⁹ and Gold⁴⁰ have also used Enovid successfully in the treatment of secondary amenorrhea. In both types of amenorrhea, it is known that a course of Enovid treatment may be followed by resumption of normal menstruation. Brown and Kistner⁴¹ state that Enovid may be similarly used for the management of oligomenorrhea and hypomenorrhea.

Let us go first to the evidence allegedly produced by Brown and Kistner, reference 41 above. This is actually what they say in the reference:

If adequate estrogen priming is present, cyclic bleeding from a secretory endometrium may be obtained by the administration of 10-20 mg. of norethindrone or norethnodrel for 20 consecutive days. Within 2-4 days after stopping the medication a bleeding episode lasting from 4 to 5 days will occur. If adequate estrogen priming has not been present bleeding will not occur and in such cases the preliminary use of an estrogen is usually necessary for an effective response. It is suggested that artificial cycles of the type be carried out for 3-4 months. Not infrequently, for reasons unknown, spontaneous menstrua-

¹²Roland, M., Smith, J. J., and Romney, S. L.: *New Synthetic Progestational Compound in Infertility*, Int. J. Fertil. 5:8-18 (Jan.-March) 1960

³⁸Kupperman, H. S., and Epstein, J. A.: *Proceedings of a Symposium on 19-Nor Progestational Steroids: Gonadotropic-Inhibiting and Uterotropic Effects of Enovid*, Chicago, Searle Research Laboratories, 1957, pp. 32-45

³⁹Roland, M.: *Proceedings of a Symposium on 19-Nor Progestational Steroids; Observations on Patients with Anovulatory Cycles and Amenorrhea When Enovid is Administered*, Chicago, Searle Research Laboratories, 1957, pp. 51-66

⁴⁰Gold, J. J.: *Proceedings of a Symposium on 19-Nor Progestational Steroids: Clinical Experience with Enovid*, Chicago, Searle Research Laboratories, 1957, pp. 86-96

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tion occurs after the progestogen-induced periods have been discontinued.

Let us notice carefully just what this says. First of all they present no data or factual evidence that their claim is true. We do not wish to doubt the observations of these outstanding investigators. In the first place they never made the claims that the Searle brochure inferred they had. The other thing they said was that their recommendation was to use it for 3 - 4 months. Based on even this quasi-evidence, one cannot then justify using it for 2 years in order to "regulate" the cycles.

The principle of the theory of this treatment is well known to gynecologists and was first described in relation to the use of estrogen and progesterone and is commonly referred to as the "rebound phenomenon."

If we now go back again to the Brown and Kistner reference 41 above, we see that they have this to say further:

Endocrine preparations are also employed to remove gonadotropic stimulation of the ovaries. The rationale of this treatment utilizes the observation that estrogenic substances, administered in large doses, block the adenohypophyseal release of the gonadotropins. Existing evidence suggests that the gonadotropic hormones are accumulated or stored in higher concentrations in the pituitary gland during this period of endocrine therapy. Cessation of the treatment, theoretically at least, releases the estrogenic blockage and results in a sudden burst of gonadotropic activity. The desired effect of this so-called rebound phenomenon is to stimulate the ovaries sufficiently to promote ovulation and normal menstrual function. *Unfortunately, the results are disappointingly poor.* [italics mine]

Let us explain at this time just what the rebound phenomenon is. This work is explained by *Enovid* in a number of publications. In essence the work was based on giving 80 sterility patients increasing doses of diethylstilbesterol for three months and increasing doses of progesterone during the same time. Thirteen of the 80 women became pregnant within 4 months of treatment. When one is dealing with sterility problems these results are astounding. *Please note at this point that the patients under discussion in this work were sterility problems and not hyper-fertility problems.* Even so, the principle of the rebound phenomenon cannot be ignored and it is only deductively reasonable that such a rebound phenomenon may result in those patients who are very irregular ovulators and menstruators. It should be re-emphasized, however, that such treatment is justified for only 3 - 4 months. No medical evidence has ever suggested 2 years or indefinite time spans, or anything more than 3 - 4 months.

Let us now return to the reference 3 in paragraph 7 which states: "Kupperman and Epstein, Roland, Smith and Hamney, Roland and Gold have also used *Enovid* successfully in the treatment of secondary amenorrhea." If one scrutinizes these articles, he finds that what these investigators discovered was that

⁴Rock, J.; Garcia, C.-R., and Pincus, G. Synthetic Progestins in the Normal Human Menstrual Cycle, in Pincus, G (editor): *Recent Progress in Hormone Research*, New York Academic Press, Inc., vol. 13, 1957, pp. 323-339

patients who have amenorrhea, if given *Enovid*, will bleed when it is withdrawn. There is no evidence offered that following cessation of therapy, menstrual periods are any more regular than previously. As a matter of fact the reference to the work of Roland reveals the following striking conclusion in his own words:

Almost all had withdrawal bleeding between two and three days after cessation of medication. The bleeding in most instances was scanty; in several this scant flow continued for eight to ten days. The six ovulatory patients had heavy bleeding with clots but it was of normal duration. Menstruation during the cycles which followed the treated ones reverted back to normal.

One assumes that when he says they reverted back to "normal," he means to what they had been previously, since they were dealing with ovulatory women. One can hardly deny that women with hyper-fertility are also ovulatory women. As we understand this, then it means that using progestins for a period of several months allows a woman to bleed at predictable intervals as long as she is being medicated, but following withdrawal of treatment, one can expect her pattern to be uninfluenced.

The above investigations of Roland and perhaps others apparently led the G. D. Searle Company to print in their brochure (3) on page 20, the following: "Ovulation in the first cycle after treatment may be delayed for three to five days or even longer; subsequent cycles will usually revert to the duration previously typical of the individual patient."

To sum up, the most liberal of medical evidence would only support the use of progestins for a period of 3 - 4 months in conditions of irregular menstruation. Even those who believe that this has merit admit that the results are disappointingly poor. These cases were women who had gone for several months without menstruating. Actually there has been no work published, to the knowledge of this author, which even attempts to show that the very fertile woman who menstruates on cycles varying from 26 to 40 days can cause these habits to change by the use of progestins. There is even evidence to support that this does not occur: the quotation of Roland above and the admission of the G. D. Searle Company who make it clear that "subsequent cycles will usually revert to the duration previously typical of the individual patient."