THE GUTERMAN TEST IN THREATENED ABORTION

A REPORT BASED ON 100 CONSECUTIVE CASES

BY

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In a recent paper (Bender, 1947) experimental work was reviewed which suggested that the administration of progesterone in the treatment of threatened abortion is indicated where there is a natural deficiency of the hormone, but that its use in the absence of progesterone deficiency is not only pointless but possibly increases the chances of the abortion progressing. This is because one of the actions of the hormone is to increase the amplitude of uterine contractions (Schultze, 1931; Moir, 1936; Henry and Browne, 1943). Accordingly, before starting specific therapy in these cases it is desirable to divide them into two categories—those accompanied by progesterone deficiency and those not so accompanied. This differentiation can be made by estimating the level of urinary pregnanediol excretion, which level is held to provide a reliable index of progesterone metabolism. The Guterman (pregnanediol excretion) test, although less exact than lengthier methods of pregnanediol assay, has been found eminently suitable for this purpose. The test has many practical advantages—it is economical and can be completed within three hours, it does not involve the use of experimental animals, and a 24-hour specimen of urine is not required, 100 ml. of a first morning specimen being sufficient. The details of the procedure, together with those of a quantitative method of assay applied to the test, are given in the paper referred to above (Bender, 1947).

Guterman (1944, 1945) originally employed the test for pregnancy diagnosis, a purpose for which, in my hands, it has not proved accurate enough to replace established biological tests. Later, Guterman (1946) reported on the use of the test in estimating the prognosis in cases of threatened abortion. Where the test was positive—i.e., the 100 ml. of urine contained more than 0.4 mg. of pregnanediol—the pregnancy continued in 30 of 34 cases, and where it was negative abortion ensued in 38 of 39 cases. The present investigation was undertaken in order to ascertain the value of the test for what seemed clinically a more fruitful purpose—namely, the determining of whether progesterone should or should not be administered in any given case of threatened abortion.

The present paper is based on a review of 100 consecutive cases diagnosed clinically as threatened abortion, including 55 already reported (Bender, 1947), in which the Guterman test was performed. In 79 cases an Aschheim-Zondek test was carried out on the same urine specimen. The follow-up in each case extended primarily for a limited period of five weeks, because the test result was significant of the urinary pregnanediol level at the time of test only. The clinical diagnosis of threatened abortion was not confirmed in all cases; in 94 the patient was or had recently been pregnant, while in 6 the condition from which the patient suffered was subsequently shown to be unassociated with pregnancy.

In 7 cases, all true threatened abortion, the test result was vitiated because progesterone had been administered within the 72 hours immediately before the collection of the urine for the test. In these a false positive result could therefore not be excluded. The remaining 93 cases fall naturally into five groups according to the final diagnoses and the test results.

Group 1 (68 Cases).—These were proved by positive Aschheim-Zondek tests and by the subsequent history and findings to have had a live pregnancy with abortion threatening at the time of the test. They can be regarded as cases of true threatened abortion. This group is subdivided into (a) those cases with a positive Guterman test (42 cases) and (b) those with a negative or weakly positive Guterman test (26 cases).

Group 2 (19 Cases).—In these cases the Guterman test was negative and the Aschheim-Zondek test was either negative or weakly positive. The clinical course in these cases confirmed that the process of abortion was already irreversible at the time of test, complete abortion having occurred in 8 cases and threatened expulsion of an already dead pregnancy being the condition in the other 11.

Group 3 (3 Cases).—The Guterman test in these cases was positive but the Aschheim-Zondek test was repeatedly negative. In each case there was present a unilateral cystic ovarian swelling which gradually regressed over a period of months, the Guterman test eventually becoming negative. These were cases of corpus luteum cysts; in one there was a history of such a cyst having been removed at laparotomy a year previously.

Group 4 (3 Cases).—In these cases both tests were negative and the conditions present were found to be unassociated with pregnancy.

The distribution of these 93 cases, together with the comparable figures of Guterman (1946) and McCormack (1946), was as follows:

Group		Bender	Guterman	McCormack
1a	Threatened abortion; positive test	42	34	0
1b	Threatened abortion; negative test	26	32	30
2	Complete or missed abortion; negative test	19	7*	0
3	Not pregnant; positive test	3	0	0
4	Not pregnant; negative test	3	0	0
		93	73	30

* These cases were included by Guterman among his total of threatened abortions with negative tests. Study of his tables shows that in all seven the simultaneously performed Friedman test was also negative. They cannot therefore be regarded as true threatened abortions, the foetus being already dead.

Results and Comment

True Threatened Abortion (Group 1a).—The method of treatment and the outcome in the 42 cases showing no evidence of progesterone deficiency as reflected in the urinary pregnanediol level were: of 11 treated with progesterone 7 aborted and 4 did not abort; of 31 not treated with progesterone 6 aborted and 25 did not abort.

True Threatened Abortion (Group 1b).—The figures in the 26 cases with evidence of progesterone deficiency showed that of 14 treated with progesterone 2 aborted and 12 did not abort; and of 12 not treated with progesterone 9 aborted and 3 did not abort.

In a series of 30 cases parallel with Group 1b McCormack's (1946) figures were: of 10 treated with progesterone 2 aborted and 8 did not abort; of 20 not treated with progesterone all aborted.

The natural corollaries of these findings are: (1) There is no indication for treating cases without progesterone deficiency (Group 1a) with the hormone; on the contrary, its administration in these cases is often followed by abortion, whereas when it is withheld spontaneous recovery occurs in the majority of cases. (2) Where there is progesterone deficiency the prompt administration of the hormone seems to avert the abortion in a large proportion of cases. When it does not it may be that the condition is already irreversible or that there are additional factors present favouring abortion. If, however, progesterone is not given to progesterone-deficient cases abortion nearly always ensues, although there is a possibility of spontaneous cure (Jones and Weil, 1938; Hain, 1942).

It may be noteworthy that 3 of the 42 cases with positive tests and 2 of the 26 cases with negative tests were

of women who had previously had three or more abortions. The figures are very small, but they may support the view that progesterone failure is not a major cause of habitual abortion.

Missed or Complete Abortion (Group 2).—The correct diagnosis in these 19 cases was established by the clinical course and by the results of simultaneously performed Aschheim-Zondek tests. This group shows the value of the simultaneous performance of pregnanediol and gonadotrophin pregnancy tests; in missed and complete abortion both are negative, while in true threatened abortion the gonadotrophin test is positive but the pregnanediol test may be positive or negative. These cases also serve as a reminder that it may be difficult, especially in early pregnancy, to differentiate between a threatened abortion and an abortion which has become complete before the patient is first seen. Finally, it becomes apparent that what is termed clinically threatened abortion includes not only true cases of that condition but also cases of threatened expulsion of a foetus already dead.

Corpus Luteum Cyst (Group 3).—In these 3 cases the positive tests reflected the increased production of progesterone by corpus luteum cysts. The correct diagnosis was established by clinical examination and by the combination of positive Guterman test with negative Aschheim-Zondek test; this affords another example of the value of performing both types of test simultaneously.

Not Pregnant (Group 4).—This group comprised 3 cases in which, as in the previous group, a period of amenorrhoea was followed by bleeding. They were cases of pelvic tuberculosis, fibroids at the menopause, and psychogenic amenorrhoea.

Discussion

The value of the Guterman test in determining the line of treatment of threatened abortion can be expressed in another way. If the above findings in respect of cases of true threatened abortion are statistically significant, as they are, then the following conclusions appear permissible.

1. In true threatened abortion 38% of cases are associated with progesterone deficiency and 62% are not. These figures correspond closely with those given by Hain (1942), who employed the lengthier but more accurate gravimetric method of assay of Venning (1937).

2. If progesterone is administered to cases in which there is no evidence of progesterone deficiency 64% abort. If, however, such cases are not treated with progesterone the abortion rate is only 20%.

3. When progesterone is given to patients in whom a low pregnanediol excretion indicates a natural deficiency of progesterone only 14% abort. If, on the other hand, progesterone is withheld in such cases the abortion rate is 75%.

4. If without any attempt at subdivision 100 consecutive cases of threatened abortion are all treated with progesterone, 45 will abort, while if none are given progesterone 41 will abort. Many clinicians are dissatisfied with the use of the hormone in cases of threatened abortion and have noted little, if any, improvement in their results since progesterone therapy was introduced. The above figures substantiate this clinical impression, and indicate that when all cases of threatened abortion are given progesterone the overall results are not likely to be any better than those obtained when no patient is so treated.

5. If, however, all cases of threatened abortion are subdivided according to their progesterone need, and progesterone is given only when the pregnanediol excretion is low, only 18% abort and a considerable salvage of foetal lives is thus made possible.

The belief that progesterone is indicated in cases of threatened abortion because it acts as a "uterine sedative" was originally based on the work of Knaus (1929). More recent work, already quoted, indicates that the hormone causes an increase in the amplitude and not an abolition

of uterine contractions. This would explain the adverse results which may follow the administration of progesterone in some cases, and during the present investigation it was in fact not infrequently observed that such administration rapidly accelerated the progress of the abortion. Where, on the other hand, the hormone has apparently relieved the threat of abortion, its action may be due to its ability to maintain the decidua and improve the foetal-maternal vascular connexions (Pincus and Werthessen, 1936).

The necessity for careful clinical examination in all cases is underlined by the fact that if there is no progesterone deficiency another cause favouring abortion must be sought; while if there is such a deficiency it may not be the only abortion-provoking factor present and abortion may then ensue despite progesterone therapy.

Summary

Investigations of 100 cases diagnosed clinically as threatened abortion were made by means of the Guterman test. In 75 the clinical diagnosis was correct. In the remainder a comparison of the results of simultaneously performed Guterman and Aschheim-Zondek tests made or confirmed the correct diagnosis. The Guterman test, although not as exact as lengthier methods of urinary pregnanediol assay, is accurate enough to differentiate those cases of true threatened abortion which are associated with evidence of progesterone failure from those which are not. In the former type of case good results can be expected from progesterone therapy, while in the latter type such treatment may accelerate the course of the abortion.

The results of this investigation suggest that the abortion rate in cases of threatened abortion where the foetus is still alive can be reduced by about 25% by selecting for progesterone therapy only those cases in which the Guterman test is negative or weakly positive.

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STATISTICAL NOTE

The 68 cases of threatened abortion were divided into two groups: Group 1a, 42 cases without progesterone deficiency, and Group 1b, 26 cases with progesterone deficiency. The difference between 42 and 34 ($68 \div 2$) is significant.

These groups were subdivided, some being treated with progesterone and the remainder not:—Group 1a: 11 cases treated with progesterone—7 aborted and 4 did not abort; 31 cases not treated with progesterone—6 aborted and 25 did not abort. Group 1b: 14 cases treated with progesterone—2 aborted and 12 did not abort; 12 cases not treated with progesterone—9 aborted and 3 did not abort.

Using Fisher's exact test for 2×2 tables on these results, we have Group 1a, $P=0.0107$; Group 1b, $P=0.00271$. These findings are statistically significant and support the conclusions that: (1) progesterone therapy prevents a probable abortion in cases with deficiency of the hormone; (2) progesterone therapy increases the chance of abortion in cases with no deficiency of the hormone; and (3) if progesterone therapy is given to all cases of threatened abortion the benefit in Group 1b tends to be cancelled out by the loss in Group 1a.

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