Human Chorionic Gonadotrophin in the Treatment of Threatened and Recurrent Abortion

A PRELIMINARY REAPPRAISAL

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SUMMARY

Early experience with the use of human chorionic gonadotrophin replacement therapy in a small number of progesterone-deficient pregnancies is presented. Twelve out of 15 pregnancies proceeded normally to term and 3 pregnancies were lost. The latter group was associated with blighted ova and a significant amount of trophoblastic tissue. The findings in this small preliminary trial appear to justify a broader controlled investigation into the value of HCG therapy in prevention of threatened or recurrent abortion associated with progesterone insufficiency.

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Progesterone insufficiency is recognised as a cause of reproductive failure, albeit very rare. The replacement of one ovarian steroid in such cases does not appear to be entirely physiological, but the replacement of a spectrum of steroids is not as yet practical. It was therefore considered that the administration of human chorionic gonadotrophin itself would produce better corpus luteum stimulation, on theoretical grounds at least, and result indirectly in better trophoblastic stimulation. In this way it was hoped to salvage cases of threatened abortion due to progesterone insufficiency. This article is a preliminary evaluation of early experience obtained with the use of human chorionic gonadotrophin (HCG) in cases of cytologically demonstrated progesterone deficiency associated with a history of (*a*) threatened abortion, and (*b*) two or more recurrent abortions.

Vaginal cytology was chosen as a method of assessment in this study, not only for reasons of simplicity and rapidity of diagnosis, but because this method has been shown to be at least as good as hormonal assay.[1,2]

PATIENTS AND METHODS

The first patient was treated in 1967. Since then, with strict selection, 15 patients have been treated during early pregnancy, 10 having a previous history of two or more early (first trimester) abortions, and 5 presenting with threatened abortion at 6 - 8 weeks' gestation.

As far as was practicable, all known possible causes for abortion were excluded. All 15 patients were clinically normal and healthy, and had negative serology tests for syphilis, negative toxoplasmosis complement fixation tests, and normal routine urinalysis, blood counts and biochemistry.

Lateral vaginal smears were cytologically examined to determine the degree of progesterone deficiency. The smears were classified good, fair and poor, according to the classification of Burton and Wachtel.[2] However, a finding of a karyopyknotic index of greater than 10% in the current pregnancy was the single most important factor in selecting patients with a previous history of early abortion for therapy with HCG.

All 15 patients had poor initial smears and were given HCG (Pregnyl; Organon) 5 000 IU by deep intramuscular injection twice weekly from the time of diagnosis (all before the 7th week of gestation, except for 1 case of threatened abortion presenting at 8 weeks) until the 16th week. If uterine growth failed to correlate with the duration of gestation, an ultrasonogram was taken at the 12th week. This was done on 4 occasions. No other drugs or vitamin supplements were administered. No advice in relation to bedrest, etc. was given.

RESULTS

The outcome of the 15 pregnancies is shown in Table I.

TABLE I. OUTCOME OF THE PREGNANCIES IN THE 15 PATIENTS TREATED

Group	No. of cases	Ultrasonogram performed	Abortion	Live infant at term
Early threatened abortion	5	2	2	3
Recurrent abortion + KPI >10%	10	2	1	9
Total	15	4	3	12

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Three of the 5 patients presenting with threatened abortion settled clinically, and the pregnancies continued successfully to term. In 2 patients the uterus failed to enlarge according to dates. An ultrasonogram in the one instance revealed a large pregnancy sac, but without evidence of a fetus. This patient underwent evacuation of the uterus under anaesthesia. The other patient aborted spontaneously. Examination of the products of conception confirmed the presence of blighted ova in both instances. A significant finding was the marked degree of trophoblastic development in relation to the pregnancy sacs, a finding which was expected in the first case from the appearance of the sac on the ultrasonogram. One patient continued to bleed for 2 weeks, but uterine growth continued and ultrasonography confirmed the presence of a normal fetus (see case 1).

Nine of the 10 patients presenting with poor vaginal smears and a previous history of early abortion proceeded successfully to term. One patient was suspected of having a twin pregnancy; an ultrasonogram revealed a single fetus and confirmed the duration of gestation. Uterine growth failed to keep pace with dates in 1 patient; ultrasonography confirmed the presence of a suspected blighted ovum (see case 2), and after uterine evacuation the significant finding once again was the marked degree of trophoblastic tissue present in relation to the size of the sac enclosing the blighted ovum.

Except for the 3 pregnancies lost because of blighted ova, the remaining 12 pregnancies proceeded to term without complication. All 12 infants were normal and healthy. No congenital abnormalities were found in this series. No abnormal drug effects were noted and no patients developed any untoward clinical effects after receiving the intramuscular HCG.

CASE REPORTS

Case 1

This 22-year-old patient presented at 6 weeks' gestation with a history of 2 previous abortions at 7 - 8 weeks' gestation. Previous investigation for a cause of reproductive failure had been negative. Vaginal smears for cytology were taken, but before assessment the patient commenced vaginal bleeding, confirmed to be uterine in origin and unassociated with uterine contractions. She was immediately hospitalised, although no active therapy was commenced for 48 hours. Thereafter the original vaginal smear was reported as showing a poor progesterone effect, and the pregnancy test was positive. HCG therapy was commenced, and bleeding ceased at 96 hours. There were no further complications during the pregnancy. At 12 weeks' gestation an ultrasonogram confirmed the presence of a high fundal insertion of a normal-looking pregnancy of about 12 weeks' duration, with the head just visible. HCG therapy was stopped at 16 weeks' gestation, and the patient was subsequently delivered of a live, normal and healthy infant at term, without further complication.

Case 2

This patient, aged 39 years, presented initially for investigation of reproductive failure. She had a previous history of 3 pregnancies, all resulting in spontaneous abortion at 8 weeks' gestation. No cause had been found. Routine investigations (thyroid function, glucose tolerance test, toxoplasmosis complement fixation test, serology for syphilis, etc.) were all negative. Shortly after investigation commenced the patient conceived spontaneously. Vaginal cytology at 6 weeks' gestation revealed a poor progesterone effect. It was decided to attempt HCG therapy and this was started from 6 weeks' gestation in the usual dosage of 5 000 IU by intramuscular injection twice weekly. At 12 weeks' gestation it was noted that the uterine size did not conform to dates, and during the next 2 weeks this lag became more marked. There was, however, no evidence of threatened abortion. At 14 weeks' gestation an ultrasonogram was taken, and this showed the presence of an empty gestational sac, but associated with profuse trophoblastic tissue. Uterine evacuation was undertaken by vacuum aspiration, and the gestational sac obtained *in toto*. Examination of the sac confirmed the presence of a blighted ovum, and excessive surrounding placental tissue.

DISCUSSION

This presentation is considered to be no more than an evaluation of early experience with the use of HCG therapy in the presence of threatened or recurrent abortion. The number of cases is small, and the results average. However, the type of case being treated, the high incidence of blighted ova in the failed cases, and the excessive amount of trophoblastic tissue present in the abortuses, do appear to justify such therapy on more than theoretical grounds, and to warrant a broader controlled investigation in a greater number of cases.

In considering the role of HCG it is, in fact, paradoxical that so large a body of knowledge could accumulate on the pharmacology and chemistry of a hormone with so little being known about its physiological action. Although the pharmacological action of HCG in unphysiological use in different animal species is relatively well understood, its physiological actions on the mother, on the fetus and on the placenta are still obscure.[3]

The history of HCG therapy in threatened abortion is of interest. Brown and Bradbury,[4] in a classic paper published in 1947, evaluated the effect of HCG therapy in normal women. Prior to their use of purified HCG, previous commercial preparations had been too bulky and had caused severe reactions. They showed HCG to produce persistence of the corpus luteum, decidual changes in the endometrium, prolonged excretion of pregnanediol, and positive Aschheim-Zondek tests on the urine. Although they suggested the use of HCG in threatened or habitual abortion they did not describe any cases with such treatment. Their work was confirmed by Fried and Rakoff[5] in 1952. The first clinical report of HCG therapy in adequate dosage appears to be that of Holund[6] in 1953, although duration of therapy was short. HCG 6 000 IU was given daily for 5 days to 47 cases of threatened abortion. Fetal salvage was achieved in 72% of the patients; nevertheless, Holund was sceptical about the value of such therapy and felt that equally good results could have been obtained with non-specific therapy.

There have been several other reports of HCG therapy, alone or in various combinations with oestrogen and progesterone.[7-9] Nevertheless, there still appear to be no adequately controlled studies of HCG therapy alone and in adequate dosage.

Hughes *et al.*[1] have stated that the information provided by vaginal cytology in predicting the eventual outcome of pregnancy in patients with threatened abortion is superior to that obtained by hormonal analyses, such as urinary oestrogen, pregnanediol and HCG assays. Although these findings have been questioned by Brown *et al.*,[10] vaginal cytology was used as a means of assessment in the present study. Following HCG therapy, vaginal smears were found to revert from highly oestrogenised to well-progestinised in several individual cases. The significance of these findings, however, will have to be tested in a larger series of cases. Nevertheless, this finding is also considered to lend some support to the use of HCG therapy at the present time.

The finding of major interest was the large amount of trophoblastic development present in cases ultimately aborting. This would add credence to the theory that the trophoblast is being well stimulated through corpus luteum support with HCG therapy. This finding alone appears to warrant the use of HCG supportive therapy in progesterone-insufficient pregnancies, and to justify further evaluation of this form of treatment in larger controlled studies.

That 3 of the pregnancies resulted in blighted ova was expected on a statistical basis.[11,12] The fact that chromosome anomalies account for a significant fetal wastage in cases of threatened and recurrent abortion[11,12] does not imply that an entirely pessimistic attitude is in order. Nor do findings such as those of Shearman and Garrett,[13] who reported as good results with placebo therapy as with progesterone replacement in 50 habitual abortion patients, entirely exclude the possibility of hormone deficiency states being aetiological factors in abortion. Such work has, however, resulted in a rather negative approach to endocrine aspects of abortion in current research. Nevertheless, further controlled investigations are still required, and it is hoped that the rationale behind HCG therapy will be further elucidated.

REFERENCES

1. Hughes, H. E., Loraine, J. A., Bell, E. T. and Layton, R. (1964): Amer. J. Obstet. Gynec., **90**, 1297.
2. Burton, E. R. and Wachtel, E. G. (1967): J. Obstet. Gynaec. Brit. Cwlth, **74**, 533.
3. Diczfalusy, E. (1961): Vitam. Horm., **16**, 229.
4. Brown, W. E. and Bradbury, J. T. (1947): Amer. J. Obstet. Gynec., **53**, 749.
5. Fried, P. H. and Rakoff, A. E. (1952): J. Clin. Endocr., **12**, 321.
6. Holund, T. (1953): Acta endocr., **12**, 61.
7. Kurzrob, R. (1946): N. Y. Med. J., **46**, 493.
8. Wilson, R. B. (1955): Amer. J. Obstet. Gynec., **69**, 614.
9. Laham, E. and Skandar, M. (1958): Ann. Endocr., **19**, 1185.
10. Brown, J. B., Evans, J. H., Beischer, N. A., Campbell, D. G. and Fortune, D. W. (1970): J. Obstet. Gynaec. Brit. Cwlth, **77**, 690.
11. Reid, D. E., Ryan, K. J. and Benirschke, K. (1972): *Principles and Management of Human Reproduction*, pp. 254 - 276. Philadelphia: W. B. Saunders.
12. Scott, J. S. *in* Dewhurst, C. J. ed. (1972): *Integrated Obstetrics and Gynaecology for Postgraduates*, pp. 207 - 225. Oxford: Blackwell.
13. Shearman, R. P. and Garrett, W. J. (1963): Brit. Med. J., **1**, 292.