

OESTROGEN THERAPY IN MISSED ABORTION AND LABOUR

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THE use of oestrogens in the treatment of missed abortion and missed labour was first suggested by Robinson, Datnow and Jeffcoate in 1935. Evidence was then produced which seemed to indicate that when the foetus is dead but retained *in utero* the inhibitory effect of progesterone is absent. The prolonged administration of oestrogen may then so sensitize the uterus that it evacuates itself either spontaneously, or in response to oxytocics such as quinine and posterior pituitary extract. Further clinical trials resulted in a report by Jeffcoate (1940) on the use of oestrogens in 55 consecutive cases of intra-uterine death of the foetus. Oestradiol benzoate was used in the earlier cases in the series and stilboestrol in the later ones with similar results. The hormone was given regularly for 5 to 8 days and was immediately followed by a quinine and oxytocin induction if abortion or labour had not occurred in the meantime. The uterus emptied itself in 87 per cent of these cases, the interval between commencement of treatment and the expulsion of the products of conception averaging 4.2 days.

Following these reports the method was widely used and accepted as the standard treatment for these conditions. It was not always successful, however, and as time passed the number of gynaecologists who questioned its value increased rather than diminished. Moreover, as knowledge of the respective actions of oestrogen and progesterone increased, the theoretical basis of the treatment became less secure. In 1950 Jeffcoate emphasized that the early experiments had not been controlled, so in the investigation reported here, carried out at his instigation, an attempt was made to control the results.

MATERIAL

The investigation was carried out at the Liverpool Maternity Hospital where, during the last 3 years, induction of labour or abortion was attempted in 45 cases of missed abortion and missed labour. Two of the treated cases were used twice in that when one method of induction failed, another was tried, thus making a total of 47 experiments in treatment. In the majority the duration of pregnancy was more than 28 weeks at the time of foetal death.

During the same 3-years period there were a further 52 cases of intra-uterine death. These were also studied but no treatment was given in this group, and all aborted or went into labour spontaneously.

METHODS OF TREATMENT

Three lines of treatment were planned, only one of which was to be followed in any particular case and the choice was made in rotation as the cases were admitted. The three programmes were as follows:

1. Stilboestrol 5 mg.
orally 4-hourly for 7 days
2. Progesterone 5 mg.
intramuscularly . . 4-hourly for 7 days
3. Sodium citrate 2 gr.
orally 4-hourly for 7 days

Sodium citrate was chosen because it seemed reasonable to believe that it had no effect on uterine action.

If labour or abortion had not started at the end of any one course of these treatments, quinine sulphate gr. 5 was given orally 3 times at hourly intervals. This was followed by intramuscular

injections of 2.5 units oxytocin at hourly intervals for 6 doses. If the pregnancy still remained *in utero* the whole course of treatment was repeated. It is recognized that so far as oestrogen is concerned heavier doses are employed in many centres, but this experiment was planned to conform to the one on which the original claims were based.

Choice of the method of treatment strictly by turn should have resulted in an equal number of cases in each group. In fact more patients received oestrogen than either progesterone or sodium citrate because, with a large and ever changing junior medical staff, a "stilboestrol induction" was sometimes automatically ordered before it was realized or remembered that this controlled investigation was in progress. There were also 2 patients in whom an oestrogen induction was attempted and failed, who subsequently received progesterone in the one case, and sodium citrate in the other.

ASSESSMENT OF RESULTS

The treatment was recorded as successful if the uterus emptied itself during or within 48 hours of concluding the two courses of treatment. Induction failed 10 times in 9 cases, 3 patients ultimately requiring curettage, 4 being treated by artificial rupture of the membranes, and 1 by abdominal hysterotomy. In the remaining 1 a "failed" stilboestrol was followed by a "successful" progesterone induction.

RESULTS

Forty-seven inductions were carried out on 45 patients and 52 cases were left untreated. The details of results are shown in Table I from which it will be seen that the overall success rate was 89 out of 99 (90 per cent). This is remarkably similar to the original 87 per cent success rate reported by Jeffcoate (1940) and suggests that the criteria adopted are comparable to those of the earlier investigation. However, the success rate with oestrogen was lower than with any other method of treatment, being 73 per cent as compared with 78.5 per cent and 91 per cent for progesterone and sodium citrate respectively. This suggests that stilboestrol has no advantage over an inert substance or over progesterone. Moreover, and bearing in mind that oestrogens

TABLE I

	Number of cases	Number successful	Average Interval. Induction-Delivery (days)	Average Length Labour (hours)
Stilboestrol ..	22	16	7.7	20.0
Progesterone	14	11(a)	10.8	17.0
Sodium Citrate	11(b)	10	6.4	16.9
No treatment	52	52		12.5

(a) Includes one success where treatment with Stilboestrol had already failed after one course.

(b) Includes one case where treatment with Stilboestrol had already failed after one course (and where Sod. Cit. also failed).

have also been used to promote better uterine action in labour, it is interesting to note that the average duration of labour after stilboestrol induction (20 hours) was longer than that when progesterone (17 hours), sodium citrate (16.9 hours), or when no treatment was given (12.5 hours).

Further analysis indicates that parity did not materially affect the overall results, although the interval between the death of the foetus *in utero* and its delivery appeared rather shorter in multiparous women. Among the treated cases there were nineteen 1-gravidae, eight 2-gravidae, nine 3-gravidae, five 4-gravidae and six 5-gravidae. In these groups the average intervals were 30, 32, 15, 25 and 23 days respectively. However, the number in each group is small, and the average time is increased by those cases in which induction failed and which were ultimately terminated by surgery.

The cause of the intra-uterine death was known in only 22 cases. Four foetuses had gross congenital abnormalities and 4 had erythroblastosis. Of the remaining 14 deaths, 12 were associated with pre-eclampsia and 2 with postmaturity. The average intervals between intra-uterine death and expulsion of the products of conception were: 19 days in the toxæmia group, 12 days for the rhesus affected babies, and 18.5 days in the case of the abnormal foetuses. The 2 postmature infants were delivered on the seventh and fourth days respectively.

The duration of pregnancy at the time of the intra-uterine death apparently did not influence

the results in regard to either the outcome of treatment or the interval between death and delivery. Counting the whole series, treated and untreated, there were 12 cases in which the pregnancy died before the 28th week and 85 after that time. The difference in the results in the two groups is not significant and this is true whether or not the patients received treatment. In the small group of 4 untreated cases in which the foetal death took place before 28 weeks, the pregnancy appeared to be longer retained in the uterus than in those of the other groups (Table II).

TABLE II
Successful Cases. Influence of Maturity

	Intra-uterine Death—Delivery Interval (days)	
	Before 28 weeks	After 28 weeks
Stilboestrol . .	30.5 (4 cases)	22.5 (12 cases)
Progesterone	22.3 (2 cases)	22.4 (9 cases)
Sodium Citrate	8.2 (2 cases)	13.7 (8 cases)
No treatment	28.3 (4 cases)	14.0 (48 cases)

THE INTERVAL BETWEEN DEATH AND DELIVERY OF THE FOETUS

Probably one of the most important findings in this investigation pertains to the interval which usually elapses between death of the foetus and its expulsion. Foetal death *in utero* is ordinarily followed by abortion or labour within a few days. When it is not, however, as in the cases forming the subject of this communication, the interval approximates 21 days (Fig. 1). Moreover this interval is the same no matter whether the

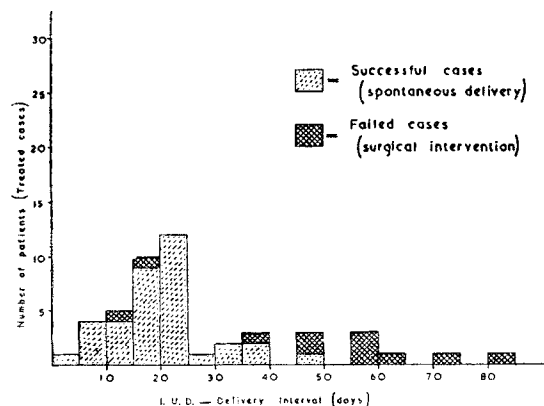


FIG. 1

case is left untreated or whether induction is attempted by medical means (Table III), and

TABLE III
Successful Cases

	I.U.D.- Induction Interval (days)	Induction- Delivery Interval (days)	I.U.D.- Delivery Interval (days)
Stilboestrol . .	16.3	7.7	24.0
Progesterone	11.4	10.8	22.2
Sodium Citrate	9.2	6.4	15.6
No treatment			21.1

this is irrespective of the method of induction employed. Indeed it would appear that observations on the time elapsing between induction and delivery are potentially misleading, and that the interval between foetal death and delivery is more constant. This again confirms that stilboestrol, and indeed the other substances employed, played little if any part in determining the occurrence and time of abortion or labour.

It follows that, in practice, it is probably unnecessary, if not unwise, to offer any treatment until a dead foetus has been retained for longer than 3 to 4 weeks.

CONCLUSION

Although the number of cases treated in this series is small, nevertheless they do strongly suggest that neither stilboestrol nor progesterone has any particular merit when used in the treatment of missed abortion and missed labour. Moreover, they also suggest that quinine and oxytocin are equally valueless because their use did not materially shorten the interval between the diagnosis of intra-uterine death and the delivery of the foetus.

We are indebted to the members of the consultant staff of the Liverpool Maternity Hospital for allowing us to conduct this investigation on their patients and to record the results. In particular we are grateful to Professor Jeffcoate under whose direction and guidance this work was performed.

REFERENCES

- Jeffcoate, T. N. A. (1940): *Lancet*, 1, 1045.
 Jeffcoate, T. N. A. (1950): *Proc. R. Soc. Med.*, 43, 734.
 Robinson, A. L., Datnow, M. M., and Jeffcoate, T. N. A. (1935): *Brit. med. J.*, 1, 749.