

USE OF DIETHYLSTILBESTROL TO PREVENT FETAL LOSS FROM COMPLICATIONS OF LATE PREGNANCY*

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THE present communication deals with further progress in a clinical evaluation of our concept concerning the action of diethylstilbestrol in human pregnancy. Analyses of results in 632 pregnancies during which this drug was given in the manner recommended by us have been reported.¹ In 491 of these cases stilbestrol was administered for the prevention or treatment of abortion. A preliminary report was included, however, upon its use in 95 patients for the purpose of preventing complications of late pregnancy. These 95 cases are included in the present study of a total of 180 women in whom the indication for therapy was diabetes, essential hypertension, nephritis or a past obstetric history of pre-eclampsia, eclampsia, premature delivery or unexplained intrauterine death of the fetus.

The use of stilbestrol in pregnancy is based upon experimental evidence for its progesterone-stimulating effect in rats² and in pregnant women.³⁻⁵ The indications for such therapy and the dosage schedule recommended have been presented.¹ We were particularly interested in its possible value for the prevention of complications of late pregnancy, since a premature deficiency of the placenta in the secretion of estrogen and progesterone before and during late-pregnancy toxemia, premature delivery and intrauterine death had been shown by our own studies and confirmed by others.⁶ We have emphasized the fact that whatever the primary etiologies of these complications may be, a premature deficiency of estrogen and progesterone sooner or later is involved and becomes an intermediate contributing factor. Moreover, we have laid emphasis upon the reciprocal relation between vascular supply to the uterus and hormonal support, adequate vascularity being as essential for the normal production of the placental steroid hormones as adequate hormonal support for the increased vascular demands of the pregnant uterus. By supplying an extra stimulus for the secretion of estrogen and progesterone, we are attempting to combat only one of the contributory factors of the final syndrome. If a more normal secretion of estrogen and progesterone is accomplished, however, the vascular deficiency should be minimized, since the combined

action of these two steroid hormones is characteristically one of vascular and myometrial growth. Experimental and clinical experience indicates that neither one of them alone could accomplish the degree of uterine growth and vascularity required in late pregnancy. Improved clinical results in themselves, therefore, would provide added support for the stimulative effect of stilbestrol upon the placental secretion of both the sex steroids.

From these considerations it is apparent that stilbestrol administration could not be expected completely to prevent late-pregnancy complications. By combating one of the contributory factors in vascular deficiency, however, we might well postpone, if not entirely avert, the onset of the final clinical abnormality. This in itself would result in less damage to the mother and a greater chance for fetal survival.

SOURCE OF CLINICAL MATERIAL

We are indebted to 58 obstetricians for the record of 104 of the 180 pregnancies to be reported, our method of acquiring this information being the same as that previously described.¹ The other 76 women were patients referred to us at the Boston Lying-in Hospital, where they received their prenatal and obstetric care. All of them took stilbestrol by mouth according to the dosage schedule used in our first study.¹ In no case was the therapy begun later than the nineteenth week and in the majority it was given from the start of the seventh to twelfth weeks. *We do not recommend diethylstilbestrol except as a preventive measure for late-pregnancy toxemia.* This statement is based on both theoretical grounds and actual experience.^{1, 4}

CLINICAL RESULTS

Table 1 presents the over-all data on the 180 women to whom stilbestrol was given to prevent late-pregnancy complications. Only 10 were primigravidas: 4 of 14 diabetic patients and 6 of 50 who had hypertension, either essential or secondary nephritis. The other 170 patients had had a total of 380 previous pregnancies, of which only 28 (7.4 per cent) had progressed normally to term with no complications involving either the mother or child. Fifteen per cent had spontaneously aborted. The other 78 per cent of previous pregnancies had been complicated by spontaneous premature delivery, unexplained stillbirth or toxemia. The tot

*Presented at the annual meeting of the Massachusetts Medical Society, Worcester, May 26, 1949.

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§E. R. Squibb and Sons supplied the 25.0-mg. tablets of stilbestrol used in this study.

fetal salvage from these 380 pregnancies had been 116 living babies, or 30 per cent.

Although the over-all outcome of the present pregnancies on stilbestrol is obviously a great improvement over the past obstetric histories, a fair evaluation of the effect of stilbestrol administration cannot be made without a more detailed analysis, as pointed out below:

In evaluating the results of stilbestrol therapy for threatened and chronic abortion,¹ we had reliable figures on the spontaneous cure rates of these conditions as a basis for statistical analysis of our data. No such generally accepted figures are available, so far as we know, as a basis for evaluating any prophylactic therapy against

TABLE 1. Data on 180 Patients Given Stilbestrol Prophylactically for Complications of Late Pregnancy (to March 1, 1949).

COMPLICATION	PAST OBSTETRIC HISTORY		PREGNANCY ON STILBESTROL	
	NO. OF CASES	PER-CENTAGE	NO. OF CASES	PER-CENTAGE
Abortions*	58	15	6	3.3
Spontaneous premature delivery†	143	38	49	27
Fetal death from prematurity	(108:75)		(16:32)	
Stillbirth (unexplained)	57	15	7	3.9
Pre-eclampsia or eclampsia	94	25	25	14
Fetal loss from toxemia	(41:43)		(4:16)	
None	28	7.4	93	52
Total living babies	116	30	147	82

*At less than 22 weeks.

†At less than 37 weeks.

complications of late pregnancy. In a planned study that is being separately reported,⁷ the course and outcome of the pregnancies of 387 primigravidas on our dosage schedule of stilbestrol are compared with those of 555 synchronous control primigravidas who received the same prenatal and obstetric care. In this study statistical analysis was possible and showed a highly significant difference between treated and control cases in the matter of the incidence and severity of toxemia and of fetal loss from late-pregnancy complications. From these results it seems safe to assume that the use of diethylstilbestrol should be effective as a preventive measure in patients in whom complications of late pregnancy may be anticipated. In evaluation of the present study on just such cases, however, certain difficulties are encountered. Lacking reliable information on spontaneous cure rates and considering the heterogeneous nature of the clinical material, we can only break down the data in various ways that seem to warrant a comparison of the outcome on stilbestrol with the past obstetric histories of the same patients.

Essential Hypertension and Nephritis

Of the 180 patients observed, 50 were given stilbestrol because of pre-existing hypertension, either

essential or secondary to renal disease. These were women either known to have essential hypertension or nephritis or found to have a blood pressure of 140 systolic, 90 diastolic, or above in at least two readings prior to the twenty-second week. The ages ranged from twenty to forty-four years, and 33 of them (66 per cent) were over thirty years old. Seven had chronic nephritis. Forty-four of these women (88 per cent) were multigravidas with poor obstetric histories. There were no twins in past deliveries, but 3 of the 50 women had twins while on stilbestrol, making a total of 53 possible infants.

By stimulation of maximum secretion of the placental steroid hormones through stilbestrol administration, it was postulated that the uterine vascular deficiency associated with hypertension might be at least partially counteracted and obstetric complications thereby minimized. The results of stilbestrol therapy are presented in Table 2 and may be evaluated by comparison with the past 105 pregnancies of these same patients when no stilbestrol was administered. Inasmuch as hypertension is a progressive disease, this means of evaluation appears to be valid.

Fetal loss was reduced from 53 to 15 per cent. Cosgrove and Chesley⁸ have placed the fetal loss in all pregnant women with essential hypertension, regardless of severity, at 38 per cent. At the Boston Lying-in Hospital between 1932 and 1948, the total fetal loss in 138 hypertensive patients was 64 per cent with a 40 per cent mortality in the 84 babies

TABLE 2. Prophylactic Administration of Stilbestrol to 50 Patients with Pre-existing Hypertension.

COMPLICATION	PAST OBSTETRIC HISTORY		PREGNANCY ON STILBESTROL*	
	NO. OF CASES	PER-CENTAGE	NO. OF CASES	PER-CENTAGE
Abortions†	24	23	4	7.5
Spontaneous premature delivery‡	29	28	13	26
Death from prematurity	(14:50)		(3:23)	
Stillbirth (unexplained)	6	5.7	0	0
Superimposed toxemia	55	52	14	28
Fetal loss from toxemia	(12:22)		(1:7)	
None	13	12	24	48
Total fetal loss	56	53	8	15*

*Including 3 twin pregnancies, making the fetal loss 8 out of 53 possible infants. There were no multiple pregnancies in the 105 cases with past obstetric histories.

†At less than 22 weeks.

‡At less than 37 weeks.

that reached viability.* Forty-nine infants of the stilbestrol-treated hypertensive patients attained viability. Only 4 of these, 8.1 per cent, were lost, as against a 40 per cent mortality among their 81 previous babies that had reached viability. It seems clear, therefore, that the fetal loss in these 50 stilbestrol-treated patients was considerably less than might have been expected. The factors involved (Table 2) are discussed below.

*We are indebted to Dr. William J. Mulligan for collecting this information from the record room of the Boston Lying-in Hospital.

The incidence of spontaneous delivery prior to the thirty-seventh week was not reduced, probably because many patients who would have aborted without stilbestrol carried their pregnancies beyond the twenty-second week but not to term. Fetal mortality from prematurity, however, was less than half that of the previous pregnancies. As shown below, there is good indication that the premature baby of a stilbestrol-treated mother is unusually mature for its gestational age.

There were 6 unexplained stillbirths in the past obstetric histories of these patients, an incidence of 5.7 per cent. No stillbirths occurred on stilbestrol.

Any rise in blood pressure during the last two months above the level noted prior to twenty-two

third, that of an infant delivered by cesarean section at thirty-one weeks because of an increase in toxic signs in a patient who had had kidney damage as well as severe hypertension (blood pressure of 210 systolic, 110 diastolic) before pregnancy began. (This was the only fetal death in this series of 50 patients that was associated with superimposed toxemia.) The past obstetric histories of all these patients, however, gave good indication that the disease was sufficiently severe to endanger pregnancy. Although the use of stilbestrol should not supplant clinical judgment in the management of hypertension complicated by pregnancy, it appears, from the results presented, that its prophylactic administration to patients in whom early interruption is not indicated reduces the incidence of superimposed toxemia (thereby minimizing further damage to the vascular system) and greatly increases the chances of obtaining a living child.

TABLE 3. Sequences of Late-Pregnancy Complications in 49 Patients with Three or More Consecutive Obstetric Complications Prior to Stilbestrol Treatment.*

COMPLICATION	PAST OBSTETRIC HISTORY		PREGNANCY ON STILBESTROL	
	NO. OF CASES	PER-CENTAGE	NO. OF CASES	PER-CENTAGE
Abortion†	53	26	2	4
Spontaneous premature delivery‡	61	29	11	22
Death from prematurity		(44:72)	2	(2:18)
Stillbirth (unexplained)	26	13	2	4
Pre-eclampsia or eclampsia	50	24	4	8
Fetal loss from toxemia		(22:44)	1	(1:25)
Bleeding in last trimester	13	6	30	61
None	7	3	42	85
Total living babies	56	27		

*At least 2 of these occurred after 22 weeks. The total number of previous pregnancies was 201.

†At less than 22 weeks.

‡At less than 37 weeks.

weeks, any albuminuria in patients with no pre-existing renal disease or increased albuminuria in those with nephritis constituted a diagnosis of superimposed toxemia. There was a significant reduction in the incidence of this complication, from 52 to 28 per cent, and an even more striking decrease in fetal mortality—there was only 1 fetal death associated with superimposed toxemia in the pregnancies when stilbestrol was being taken, an incidence of 7 per cent, whereas 12, or 22 per cent, of their previous 55 toxic pregnancies had resulted in loss of the infant.

Finally, the past history of these patients had only 13 uncomplicated pregnancies, an incidence of 12 per cent, whereas nearly half the same patients, when given stilbestrol from early in pregnancy, delivered at term with no obstetric complications whatsoever.

The gratifying results in these 50 patients should be moderated by the explanation that only 12 of them had diastolic pressures above 100 prior to the twenty-second week, these being the only ones in whom the severity of the pre-existing disease might have made early interruption advisable. In these 12 cases there were 3 fetal deaths, 1 due to spontaneous abortion at twenty weeks, 1 to spontaneous premature delivery at twenty-six weeks and the

Sequences of Late-Pregnancy Complications

Of the 180 women to whom stilbestrol was given for the prevention of complications of late pregnancy, 49 had had 3 or more previous consecutive pregnancies that had been complicated by some abnormality associated with a deficiency of the placental steroid hormones. There were a number of abortions in the over-all past-histories, but the last 3 pregnancies of each patient had included at least 2 in which complications developed after the twenty-second week. Forty-four of these women (90 per cent) had never had a full-term, uncomplicated pregnancy, although none of them had had less than 3 previous gestations and the average number was 4.3. Considering the repetitive nature of late-pregnancy complications in this group of women, it seems valid to base evaluation of stilbestrol treatment upon a comparison with their past obstetric histories. Such a comparison is presented in Table 3.

Although spontaneous abortion was markedly lowered, there was no significant reduction in the incidence of spontaneous premature delivery, possibly because patients who would have aborted without stilbestrol progressed beyond the twenty-second week, but were still unable to carry on to term. Fetal loss from prematurity, however, was reduced from 72 to 18 per cent. The factors that appear to be operative in the reduction of fetal mortality from prematurity when stilbestrol is given are discussed below.

Of the 145 fetal deaths in the previous pregnancies of these patients, 26 were accountable to unexplained stillbirths. The incidence of this abnormality was considerably reduced, from 13 per cent in the previous pregnancies to 4 per cent when stilbestrol was administered.

Twenty-three of the 49 women had had pre-eclampsia or eclampsia (2 cases) in previous pregnancies, with a total of 50 late-pregnancy toxemias

in the past obstetric histories. Fourteen women had had this complication in at least 2 consecutive pregnancies prior to the one in which stilbestrol was given. There was no eclampsia on stilbestrol. The incidence of toxemia was reduced from 24 per cent in the past obstetric histories to 8 per cent on stilbestrol, and the fetal mortality associated with this disease from 44 to 25 per cent.

A small number of the previous pregnancies of these 49 women (6 per cent) had been complicated by bleeding during the last trimester. Only one (2 per cent) had this abnormality on stilbestrol.

Finally, on stilbestrol, 30 of these women (61 per cent) went through pregnancy to term with no complications whatsoever, whereas only 7 per cent of the previous 201 pregnancies had been uncomplicated. Forty-two of them (85 per cent) gave birth to children that lived, as against only a 27 per cent fetal salvage in the past obstetric histories. Of these 49 women, all of whom had had 3 or more previous pregnancies, 17 had no living children

was 4, or 28 per cent, which is high but is a distinct improvement.

Among our records on 804 "obstetric problem cases," including the 66 referred to above, in which stilbestrol was given according to our dosage schedule for complications of early or late pregnancy, there was a total of 65 cases in which late-pregnancy toxemia was diagnosed. The 14 cases discussed above were the only ones in patients who had a previous history of toxemia, and the only fetal deaths were the 4 that occurred in these patients — an over-all fetal mortality from toxemia of 6.2 per cent. This is an impressive figure only when one considers that in all these women obstetric difficulties were anticipated and that 43 per cent of the 94 toxic pregnancies of their past obstetric histories had resulted in death of the fetus.

Spontaneous Premature Delivery

Prematurity accounts for more fetal deaths than any other single obstetric abnormality except abor-

TABLE 4. Results of Prophylactic Stilbestrol Treatment for Premature Delivery on the Basis of Past Obstetric History.

No. OF PREVIOUS PREMATURE DELIVERIES	No. OF PATIENTS	No. OF PREVIOUS PREGNANCIES	PREMATURE DELIVERIES		FETAL DEATHS FROM PREMATURE DELIVERIES		PREMATURE DELIVERIES ON STILBESTROL		FETAL DEATHS FROM PREMATURE DELIVERIES ON STILBESTROL	
			NO.	PER-CENTAGE	NO.	PER-CENTAGE	NO.	PER-CENTAGE	NO.	PER-CENTAGE
1	36	56	36	65	32	89	15	41	7	47
2	22	46	44	96	32	73	13	59	5	37
3	12	41	36	88	27	75	6	50	2	33
4 or more	6	29	27	93	17	63	3	50	1	33
Totals*	76	172	143		108		37		15	
Averages				83		76		49		40

*The total of fetal deaths was 133 among 172 previous pregnancies (77%) and 15 among 76 pregnancies on stilbestrol. There were 25 abortions in the past obstetric histories and none on stilbestrol.

prior to the administration of stilbestrol. Twelve of these, or 71 per cent, now have living and well babies.

Pre-eclampsia and Eclampsia

Of the 180 women being reported, 66 had had a total of 94 toxic pregnancies prior to the one in which stilbestrol was administered. Eight of these had had eclampsia. The results of a very extensive study of toxemia by Mastboom, of Amsterdam,⁹ revealed 30 per cent and 56 per cent recurrence of toxemia after a previous eclampsia and pre-eclampsia, respectively. Accordingly, 35 of these 66 women, or 53 per cent, would have been expected to have toxemia in the pregnancy in which stilbestrol was given. Actually, only 14, or 21 per cent had this complication — a highly significant reduction if Mastboom's figures are acceptable in this country.

In the 94 previous toxic pregnancies there were 41 fetal deaths — a mortality of 43 per cent. In the 14 toxic pregnancies that the same patients had despite stilbestrol, the fetal loss from toxemia

Of the 180 women treated for the prevention of late-pregnancy complications, 76 had a history of spontaneous premature delivery. In this category we are omitting stillbirths and premature delivery associated with toxemia. One hundred and forty-three (83 per cent) of the previous 172 fetuses had been born alive spontaneously between the twenty-second and thirty-seventh weeks, and 108 of these (76 per cent) had died of prematurity.

In Table 4 these patients are grouped according to the number of premature deliveries that they had had prior to the pregnancy in which stilbestrol was prophylactically administered. In each group there was a considerable decrease in the incidence of prematurity, but, as has been pointed out elsewhere,^{1,7} about half the women who tend to deliver early cannot be carried to term on stilbestrol. This suggests that in half these cases the primary etiology lies in some abnormality that cannot be entirely counteracted by stilbestrol administration. We have repeatedly emphasized the reciprocal relation that exists between the vascular supply to the uterus and the secretion of the placental steroid

hormones, estrogen and progesterone. Adequate vascularity depends upon adequate hormonal support, but any condition that adversely affects the blood supply to the uterus has a detrimental effect upon the production and metabolism of the placental steroid hormones. An inherent hypertonicity of the uterus, for example, could readily interfere with a completely normal secretion of estrogen and progesterone even when the extra stimulation for such secretion, which we believe to be supplied by stilbestrol administration, is provided. It seems probable that the tendency to deliver early can often be ascribed to some such mechanical interference with blood supply to the growing products of conception.

Despite the fact that half these 76 women delivered early even when taking stilbestrol, 80 per cent of them gave birth to living and well babies, whereas less than a quarter of their previous 172 pregnancies had terminated in living children. This marked improvement in fetal salvage may be accounted to the fact that along with the reduction in the incidence of premature delivery there was a considerable reduction in fetal loss from prematurity (Table 4). This is apparent in all groups regardless of the number of previous premature deliveries. As clinical results have accumulated, the impression has grown that the premature babies of stilbestrol-treated mothers are exceptionally large and "rugged"

TABLE 5. Incidence of Prematurity in 1191 Patients on Stilbestrol.

TYPE OF PATIENT	TOTAL INFANTS DELIVERED NO. OF CASES	14 DAYS OR MORE BEFORE TERM		INFANTS WEIGHING 2500 GM. OR LESS	
		NO.	PER- CENTAGE	NO.	PER- CENTAGE
Normal primigravidas	387	46	12	11	2.8
Obstetric problem cases	804	127	16	115	13.6
Totals	1191	173		126	
Averages			14.6		10.5

for their gestational ages. This impression is borne out by the following analysis of our data.

Premature Babies of Stilbestrol-Treated Mothers

The definition of prematurity accepted by the American Academy of Pediatrics¹⁰ is "any infant born alive who weighs 2500 gm. (5 pounds, 8 ounces) or less." In presenting our data we have purposely adhered to gestational age rather than weight, partly because the past obstetric histories often gave no information concerning weights of infants and therefore no means of comparison, and partly because so many of the prematurely born infants of stilbestrol-treated mothers weighed more than 5½ pounds. To determine just what effect stilbestrol had upon babies born early, we have analyzed our data concerning all those delivered fourteen days or more before term by 1191 women (to

March 1, 1949) who took stilbestrol during pregnancy according to our dosage schedules. Three hundred and eighty-seven of these were primigravidas at the Boston Lying-in Hospital, a part of a twenty-one-month study in which alternate normal primigravidas were treated so that results could be compared with a group of synchronous controls receiving the same prenatal care.⁷ The other 804 patients were treated either for threatened abortion or prophylactically for the prevention of early or late obstetric complications that might have

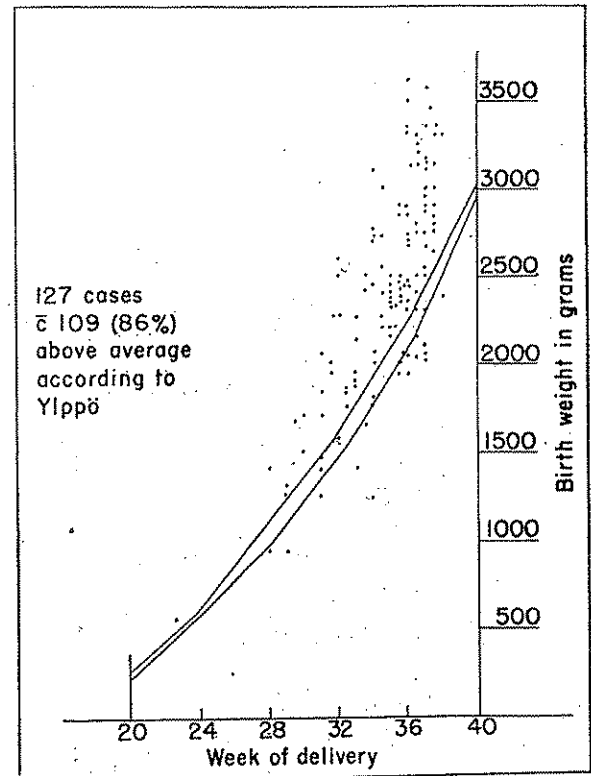


FIGURE 1. Birth Weights of Infants Born More Than Fourteen Days before Estimated Date of Confinement (Omitting Twins and Diabetic Patients).

been anticipated in view of their medical or past obstetric histories. For the sake of brevity these 804 patients are termed "obstetric problem cases." All live-born infants delivered two weeks or more before term are included, whether or not the pregnancy was normal or the delivery spontaneous.

In Table 5 the incidence of prematurity is presented on the basis both of dates and of birth weights. In the normal primigravidas the incidence of prematurity was only 2.8 per cent according to birth weight, whereas 12 per cent were born early. In the obstetric problem cases, as might be expected, the definition of prematurity had a less marked influence upon the percentage incidence, since more of these women delivered very early and had small infants. That most of their babies were large for their gestational ages, however, is

shown in Fig. 1 and 2, in which scattergrams for the length and weight are presented in relation to curves based on averages. The upper curve in both these charts was determined by Ylppö in 1919 and the lower by Scammon and Calkins between 1922 and 1925.¹¹ Of the 127 babies born fourteen days or more before term, 109 (86 per cent) were above average in weight. Unfortunately, accurate data on the crown-heel length were available in only 41 cases, but 37 of these (90 per cent) fell above the average curve. In the series of 387 primigravidas at the Boston Lying-in Hospital (a study being reported elsewhere⁷), over 90 per cent of the

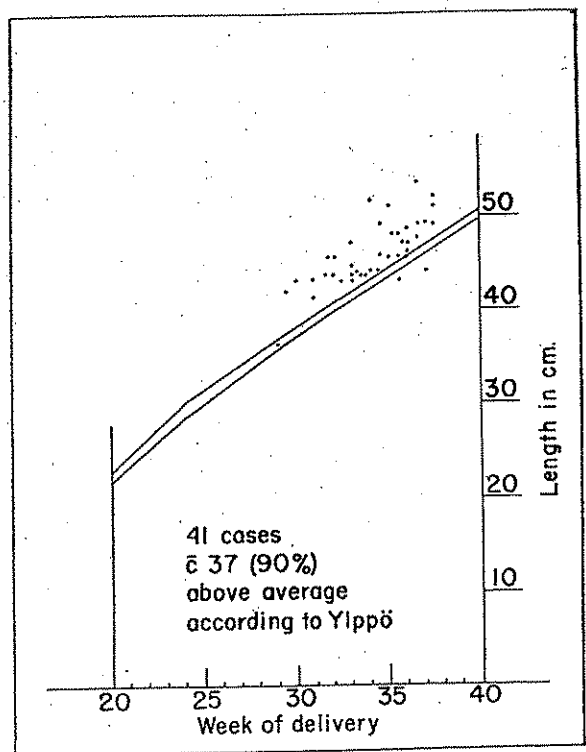


FIGURE 2. Available Information on Crown-Heel Length of Infants Born More Than Fourteen Days before Estimated Date of Confinement.

41 premature infants of treated patients fell above the average curves for both weight and length, whereas in the synchronous control group of 63 premature babies of 555 primigravidas who received no stilbestrol the figure was 60 per cent. If these average curves are applicable to the present-day population, one would expect a scattergram of controls to fall 50 per cent above and 50 per cent below the lines. Sixty per cent above the average in a scattergram of 63 control cases is not a significant deviation. We may assume, therefore, that the upper curves for weight and length of Ylppö (1919) still provide a sound basis for evaluation.

This evidence for the greater size and maturity of premature babies delivered to stilbestrol-treated mothers seemed sufficient explanation for their greater chances for survival. It was of interest to discover, however, how our mortality rate in infants weighing 2500 gm. or less would compare with vital statistics on premature infants as a whole.

TABLE 6. Mortality in Premature Infants.*

HOSPITAL	DATES	NO. OF PREMATURE INFANTS*	MORTALITY %
Sarah Morris Hospital, Chicago ..	1940-45	1993	25.8
Boston Lying-in Hospital	1943-45	481	15.0
Charity Hospital, New Orleans ..	1944-45	1122	27.4
New York Hospital, Pediatric Department	1943-45	506	22.3
Long Island College Hospital, Brooklyn, Pediatric Department	1940-45	635	16.1
Stilbestrol-treated mothers (1191 cases) — Smith and Smith dosage schedule	1943-48	126	6.3

*Weight of 2500 gm. or less.

Among 1191 deliveries of stilbestrol-treated mothers there were 126 babies weighing 2500 gm. (5 pounds, 8 ounces) or less. Eight of these, or 6.3 per cent, died. In Table 6 this figure is compared with similar statistics from a number of hospitals* and is shown to be very significantly lower than that of the Boston Lying-in Hospital, the lowest of the group. This could be due, of course, to fewer very small babies born to the mothers who had taken stilbestrol. That this is not the explanation, however, is shown in Table 7, in which the total fetal mortality is broken down into groups according to birth weight

TABLE 7. Distribution of Birth and Mortality Rates in Premature Infants.*

BIRTH WEIGHT	BOSTON LYING-IN HOSPITAL (1944-1948)		STILBESTROL-TREATED MOTHERS (1943-1948)	
	TOTAL PREMATURE INFANTS	MORTALITY %	TOTAL PREMATURE INFANTS	MORTALITY %
gm.	%	%	%	%
1000 or less	6	92	2.4	67.0
1001-1500	10	58	11.6	20.0
1501-2000	22	13	27.0	5.9
2001-2500	62	5	59.0	1.3
Totals	817		126	
Averages		16		6.3

*Weight of 2500 gm. or less.

and the results compared with similar figures from the Boston Lying-in Hospital for the years 1944-1948.* In each weight group the fetal mortality is lower than that at the Boston Lying-in Hospital. The indication is, therefore, that regardless of size, the babies of stilbestrol-treated patients are more likely to survive.

In a 1948 publication by Koch, Weymuller and James,¹² the following statement was made: "Mortality from premature birth can obviously be re-

*We are indebted to Dr. Stewart H. Clifford, associate in pediatrics, Harvard Medical School, for the vital statistics on premature infants used, and for advice in analyzing our data.

duced in but two ways, either by an actual over-all reduction in the incidence of premature birth or by improvement in methods of care of the premature infant after birth." It appears from the figures presented above on the babies of stilbestrol-treated mothers that a third way of reducing fetal mortality from premature delivery should be added to this statement—namely, by improving the vascular supply to the uterus and thereby providing a better maternal environment for the fetus so that even if it is delivered prematurely it will be in better condition and actually more mature than would be expected from its gestational age. The administration of stilbestrol as a prophylactic measure appears to be one way in which this may be accomplished. Our interpretation is that even in cases in which the primary cause of premature delivery cannot be counteracted, the placental secretion of estrogen and progesterone is stimulated to its maximum capacity up to the time when non-hormonal factors gain the supremacy and bring on the vascular and hormonal deficiency associated with the onset of labor.⁶

SUMMARY

The progress and outcome of pregnancy in 180 women to whom stilbestrol was administered for the prevention of late-pregnancy complications are reported. In the evaluation of results we have relied largely upon grouping the cases in various manners so that the outcome on stilbestrol could be compared with the past obstetric histories of the same patients. All but 10 of them were multigravidas with a total of 380 previous pregnancies, only 7.5 per cent of which had been normal. Fifteen per cent of their previous pregnancies had terminated in spontaneous abortion. The other 78 per cent had been complicated by spontaneous premature delivery, unexplained stillbirth or toxemia.

Fifty women had pre-existing hypertension, either essential or secondary to renal disease. In the past obstetric histories of 105 pregnancies (no twins), there had been a 23 per cent fetal loss from spontaneous abortion and a further 30 per cent fetal loss from late-pregnancy accidents. On stilbestrol there were 3 twin pregnancies making a total of 53 fetuses. Four of these (7.5 per cent) were aborted, and another 4 (7.5 per cent) lost after the period of viability. The factors operative in the reduction in fetal mortality during later pregnancy were a lowered incidence of superimposed toxemia and of unexplained stillbirth and a decrease in fetal mortality in prematurely delivered infants.

Forty-nine patients had had a sequence of 3 or more consecutive pregnancies prior to stilbestrol in which complications associated with progesterone

deficiency had occurred. In at least 2 of the 3 the abnormalities had developed after the period of viability. Only 3 per cent of the previous 201 pregnancies had been normal, and only 27 per cent of the offspring had survived. On stilbestrol 61 per cent of patients had no obstetric complications, and 85 per cent gave birth to living children.

Sixty-six women had had pre-eclampsia or eclampsia in 94 of their previous pregnancies, with 41 fetal deaths, a mortality rate of 43 per cent from this disease. According to Mastboom, 35 of these 66 women would have been expected to have toxemia in the pregnancy in which stilbestrol was given. Actually, only 14 of them had this complication with a 28 per cent fetal mortality. Among our records on 804 "obstetric problem cases" in which stilbestrol was administered for one reason or another there were 65 toxic pregnancies including these 14. The over-all fetal mortality from toxemia on stilbestrol was 6.2 per cent, as against 43 per cent in the past obstetric histories of the same patients.

Seventy-six women had had spontaneous premature delivery in 83 per cent of their pregnancies prior to the one in which stilbestrol was given. Forty-nine per cent again delivered prematurely despite stilbestrol administration. The fetal loss, however, was reduced from 77 per cent in the past obstetric histories to 20 per cent on stilbestrol.

Analysis of our over-all data on the prematurely delivered infants of stilbestrol-treated mothers indicates that these babies are exceptionally heavy and long for their gestational ages and that, regardless of size, more of them survived than would have been expected from recent statistics on the mortality rates of premature infants.

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