BRITISH MEDICAL JOURNAL

LONDON SATURDAY MAY 8 1937

THE HABITUAL ABORTION AND STILLBIRTH SYNDROME AND LATE PREGNANCY TOXAEMIA VITAMIN E AND THE PROLAN-PROGESTERONE MECHANISM

BY

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In previous communications I have published evidence for the view that the factors responsible for late pregnancy toxæmia tend, in a high proportion of the other pregnancies of women so susceptible, to cause abortion, accidental hæmorrhage, etc., without toxæmia (Young, 1914, et seq.). From a study of the reproductive history of 220 successive cases of toxæmia at the Edinburgh Royal Maternity Hospital I (1927) concluded "that women with an eclamptic history commonly have resident within their body some morbid influence, which is not inconsistent with good health between their pregnancies, but which is inconsistent with the normal continuance of pregnancy to term. Many of the damaged pregnancies in such women end in abortion, some end in premature birth or stillbirth, but only in comparatively few such pregnancies does this constant and imminent x factor culminate in a toxæmic attack."

TABLE I.—*The Habitual Abortion and Stillbirth Syndrome in Toxaemia*

Case	Pregnancy	Case	Pregnancy
1 (1543)	(1-7) Normal (8-10) Abortion (11) Eclampsia	6 (1442)	(1-2) Normal (3) Premature stillbirth. No toxæmia (4) Eclampsia
2 (827)	(1-2) Normal (3-7) Abortion (8) Eclampsia	7 (1393)	(1) Full term. Toxæmia (2) Accidental hæmorrhage. Premature stillbirth. No toxæmia
3 (1551)	(1-2) Abortion (3) Eclampsia	8 (1312)	(1) Normal (2) Abortion. No toxæmia (3) Accidental hæmorrhage. Premature stillbirth. Toxæmia (4) Accidental hæmorrhage. Premature stillbirth. No toxæmia
4 (1764)	(1) Normal (2) Premature live birth (3) Normal ? (4) Stillbirth (5) Premature live birth (6) Eclampsia		
5 (1422)	(1) Premature stillbirth (2-3) Abortion (4) Eclampsia		

In Table I, which represents the reproductive history of cases selected from a large number of similar clinical records, these facts are brought out in a striking manner. They exhibit the frequently recurring nature of the phenomenon and demonstrate that this may begin with the first pregnancy or, alternatively, it may only appear during subsequent pregnancies as an "acquired" taint. Further, they bring out the important circumstance that the toxæmic element, in general, only obtrudes itself where the damaged pregnancy has advanced to the later

months. For a fuller study of these questions and for the data on which we have built up the hypothesis of placental intoxication in an attempt to correlate the clinicopathological data embraced within the toxæmia phenomenon the reader is referred to the previous papers mentioned. These papers also present evidence for the contention that the common attribution of the recurring obstetric disasters of such women to a persisting "nephritic" factor (chronic nephritis, low reserve kidney, etc.) has for long diverted attention from the realities of the situation and has sterilized much sincere effort directed to the elucidation of primary factors.

The X Factor and Recent Discoveries

Recent investigations have opened out to us a possible new avenue of approach in our search for the missing factor in the habitual abortion-stillbirth-toxæmia syndrome. This evidence has come from two directions. In the first place, since Wiesner (1931) showed that a negative A.-Z. reaction in a living pregnancy implied a high risk of abortion or premature birth, the luteinizing factor obtained from pregnancy urine or the corpus luteum hormone itself has been used with considerable success in the treatment of habitual abortion (Johnstone *et al.*, 1932; Krohn *et al.*, 1935; Kane, 1936). We have ourselves the completed and consecutive histories of seventeen women who between them had fifty-one successive pregnancies ending in abortion, premature stillbirth, stillbirth, or early neo-natal death before coming under treatment. In seventeen subsequent pregnancies under treatment with urinary prolan there were fifteen which ended in the birth of a surviving child—that is, a 100 per cent. failure was transformed into an 88.2 per cent. success. The circumstances attending the administration of prolan and progesterone strongly suggest that it operates in the form of a true substitution therapy. At the same time the pregnancy gonadotropic test may be positive in cases which respond to the therapy, and this makes it necessary for us, in the absence of quantitative data, to exercise caution in our interpretation of the phenomena. This attitude of caution is all the more necessary in that successful therapy is obtained with a unit dose of hormone which is infinitesimal in comparison with the quantities known to exist in normal pregnancy. Thus, whereas 100 rat units of prolan twice weekly may be clinically sufficient, it is known that the excretion of this hormone in healthy pregnancy reaches several and often many thousands of rat units per litre of urine.

Significance of the Results

In Tables II, III, and IV we have collated our personal cases, completed and otherwise. To appreciate the full significance of these results it is important to recognize that, in so far as they refer to women who present themselves for treatment because of their history of recurring obstetric disaster, we can naturally to a large extent eliminate from the history such irrelevant causes of repeated abortion as intentional interference. Indeed, in the majority of instances their failure to carry is to such women a source of great distress. Further, it is to be noted that in all cases the Wassermann reaction is proved to be negative and there is no detectable pathology to account for their symptoms, such as retroflexion and deep cervical laceration.

The second important line of advance is based upon the recognition of the part which essential food substances play in the nutritional maintenance of the pregnant state.

TABLE II.—*Habitual Abortion, etc. Pregnancy Test Negative*

Case No.	Age	Previous Pregnancies	Present Pregnancy
1 (O.P.)	33	(1) 7 mths. Lived 2 days (2) F.T. " 1½ "	A.-Z. — 16 weeks Full-time Child alive and well
2 (X. A.)(210)	19	(1) 2 mths. Abortion (2) 5 " "	A.-Z. — 8 weeks Full-time Child alive and well
3 (2486)	25	(1) 3 " " (2) 3 " "	Friedman — 12 weeks Full-time Child alive and well
4 (A. N. C.) (192)	41	(1) 2 " " (2) 3 " "	Friedman — 12 weeks Progressing at 25 weeks
5 (307)	23	(1) F.T. Alive and well (2) 3 mths.	Friedman — 20 weeks Progressing at 28 weeks
6 (6608)	24	(1) F.T. Alive and well (2) 4 mths. Twins (3) 8 " S.B. Hydrocephalus Macerated	Friedman — 24 weeks Progressing at 29 weeks
7 (11321)	26	(1) 8 " Died 28 hrs. (2) 7 " " 8 hrs.	Friedman — 27 weeks Progressing normally at 33 weeks Toxaemic symptoms developed at 27th week. Controlled ? by prolan

TABLE III.—*Habitual Abortion, etc. Pregnancy Test Positive or not Made*

Case No.	Age	Previous Pregnancies	Present Pregnancy
1 (H. 434)	27	(1) 4 mths. (2) 3 " "	Treatment from 6th week Full-time Child alive and well
2 (O. P.)	28	(1) 7 " Lived 3 hrs. (2) " " 3 days	A.-Z. + Treatment from 3rd month Full-time Child alive and well
3 (F. 803)	31	(1) 37 wks. Alive and well (2) 7 mths. Lived 1½ hrs. (3) 7 " " 1½ " A.P.H. (4) 6 " " 6 days	Treatment from 3rd month 38 weeks Child died, 10 days
4 (O. P.)	24	(1) 1 mth. (2) 2 mths. (3) 3 " "	A.-Z. + Treatment from 6th week Full-time Child alive and well
5 (O. P.)	28	(1) 3 " " (2) 4 " " (3) 6½ " "	A.-Z. + Treatment from 6th week 5/12 abortion
6 (O. P.)	25	(1) 3 " " (2) 3 " "	A.-Z. + Treatment from 3rd month Full-time Child alive and well
7 (O. P.)	38	(1) F.T. Alive and well (2) F.T. " " (3) 8 mths. " S.B. " (4) 3 " " (5) F.T. S.B.	Treatment from 5th month Full-time Child alive and well

In lower animals it has for long been known that the reproductive processes are sensitive to dietetic influences and that imperfect feeding may in a variety of ways disturb the fertility of the animal by leading to sterility or to interference with the growth of the foetus in the uterus. Vitamins A and E would seem to occupy a special place in the reproductive processes, in that gross deprivation of either, whilst consistent with apparently normal health of the mother animal, is attended by serious interference with the intra-uterine development of the foetus. So far, no adequate attempts have been made to assess the possible significance of the vitamin A factor in human pregnancy, but there is now a considerable body of evidence in respect of vitamin E. The work of Evans and his collaborators (Evans and Burr, 1927; Evans, 1932) on the specific relation between vitamin E deficiency and a form of "habitual abortion" in lower animals has inspired the use of this vitamin in human pathology. In rats (and the same facts have been shown to apply to some other animals) gross deficiency in E, without disturbing the general health and vigour of the animal, and without affecting oestrus and the faculty of fertilization, leads to a progressive disturbance in the nutrition of the foetal placenta and to maceration and resorption of the foetuses in the uterus. Vitamin E administered during the earliest stages of pregnancy is capable of anticipating and preventing this foetal destruction, but, after the critical phase of placentation, replacement of vitamin E is valueless. Congestive and haemorrhagic changes of a secondary nature occur in the maternal placenta of such affected gestations, and this is associated with vaginal bleeding. Whilst analogies drawn from animal pathology are apt to be an insecure basis for argument, it cannot but be regarded as suggestive that, in the case of the x factor that constitutes the background of the human problem and the E deficiency as it affects the animal, there are three striking points in common: first, the general health of the host remains apparently normal; secondly, repeated and often rapidly succeeding mating and impregnation is the rule; thirdly, the successive pregnancies are blighted. To these three admittedly striking analogies we have to add a fourth, the fact that in each case the exhibition of a preparation containing vitamin E (wheat-germ oil) at a sufficiently early stage breaks the sequence and, in a large proportion, enables the normal carrying of the pregnancy to full term. There is now considerable evidence in the literature (Vogt-Möller, 1931, 1933; Juhasz-Schäffer, 1933; Watson and Tew, 1936) as to the efficacy of wheat-germ oil in habitual abortion and stillbirth in women, and Shute (1937) has employed it with success in cases of accidental ante-partum bleeding.

The outstanding nature of the progress to which these discoveries witness can be best realized by those who recall the hopelessness with which the subject of habitual abortion and stillbirth was regarded in former days. Writing in the 1917 edition of his textbook, Whitridge Williams (1917) expressed the views then current when he said: ". . . nor will the most extended clinical study give a clue to the cause, and consequently the treatment of such patients is empirical and altogether unscientific." And again: ". . . the treatment of repeated abortion is in general so unsatisfactory as to constitute one of the opprobria of obstetrics."

It remains for the future to establish a correlation between two discoveries which have so strikingly and so unexpectedly converged towards the solution of one of our most baffling clinical problems. Meanwhile, the available data are consistent with the view that vitamin E possesses specific significance for the nutrition of the

TABLE IV.—*Habitual Abortion, etc., and Toxaemia and Ante-partum Haemorrhage*

Case No.	Age	Previous Pregnancies	Present Pregnancy				
			Pregnancy Test	Treatment commenced	Ante-partum Bleeding	Toxaemia	Result to Child
1 (A. 445)	37	(1) 7 mths. Induction for toxaemia (2) 7 " Spontaneous. Toxaemia. Lived 2 days		5th month	Nil	37th week albuminuria B.P. 140/90	Induction 38th week Alive and well
2 (H. 427)	31	(1) 6 " " (2) 3 " "	A.Z. +	3rd month	3rd month	39th week albuminuria, oedema	Full-time Alive and well
3 (O. P.)	31	(1) F.T. Alive and well (2) F.T. Died 4 days (3) 2 mths. (4) 3 " " (5) 2 " " (6) 3 " "	A.Z. +	4th month	3rd and 4th months	Nil	Full-time Alive and well
4 (O. P.)	23	(1) 3 " " (2) 5 " " (3) 3 " "		3rd month	8th month	Nil	Twins. Full-time. 1 alive and well. 1 died 10 days—convulsions
5 (R. M. H.)	40	(1) 3 " " (2) 3 " " (3) 5 " "		3rd month	4th month	38th week albuminuria B.P. 145/90	Full-time Alive and well
6 (P. C.)	36	(1) 2 " " (2) 2 " " (3) 4 " " (4) 7 " " Hyperemesis Severe toxaemia, albumi- nuria, jaundice, coma (5) 3 " " (6) 5 " " Placenta praevia (7) 6 " "		Early months	Nil	Nil	Full-time Alive and well
7 (9774)	23	(1) F.T. S.B. (2) F.T. Lived few hours (3) F.T. Lived 1 week	Friedman +	7th month	2nd to 8th month	Vomiting. Albuminuria B.P. 140/90	Full-time Alive and well
8 (11321)	26	(1) 8 mths. Died 28 hours (2) 7 " " Died 8 hours	Friedman -	7th month	Nil	27th week Headaches, visual dis- turbances	Progressing normally at 8th month Toxaemic symptoms subsided

placenta, and that, in some manner which is not clear, it operates through the activation of the luteinizing mechanism. The problem is complicated by several physiological uncertainties regarding the site of origin of prolactin and progesterone in human pregnancy, which are not directly germane to the subject of this paper. It is generally believed that during the pregravid and the early gravid periods the anterior pituitary is responsible for the elaboration of the luteinizing hormone and the ovary for the production of progesterone, but that in the human subject this dual function is during the later stages of pregnancy performed by the placenta. We have no means of knowing which part or parts of the placenta are concerned in this reciprocal action. From the large output of the luteinizing substance in hydatid mole and chorion epithelioma we might by analogy be justified in ascribing the source of this hormone to the *foetal* elements of the placenta in ordinary pregnancy. From the excessive formation of luteal tissue which in these abnormal chorionic states may take place in the extrachorionic or maternal tissue of the ovary, we might by analogy ascribe the source of the luteal hormone to the *maternal* placenta in an ordinary pregnancy. If it could be established that the two hormones spring from different biological sources in the placenta it would be interesting to speculate whether vitamin E bears any special and differential relation in regard to the tissues concerned. In this connexion some recent observations on the effect of vitamin E deficiency on the gonadotropic functions of the anterior pituitary possess a special interest. It has been shown (Rowlands and Singer, 1936) that the pituitaries of rats fed on an E-free diet are markedly defective in the luteinizing or ovulation-producing hormone as tested on oestrous rabbits. At the same time neither anterior pituitary nor luteinizing pregnancy urine extracts are capable of preventing the resorption of the foetuses in an E-free rat (Diakov and Krizenecky, 1933; Geller, 1933; Rowlands and Singer, 1936).

Toxaemia and the X Factor

While there is still some uncertainty in regard to the interpretation of the scientific data, there would seem to be no room for doubting that these recent discoveries have brought us within measurable distance of a solution of the habitual abortion-stillbirth complex in women. The fact that we can eradicate the underlying taint in a percentage which in different records varies between 75 and nearly 90, and that the earlier the treatment is instituted the higher the success, helps to establish this claim on a secure basis. In view of the significant part which we have shown a habitual abortion-stillbirth sequence to play in the toxaemic phenomena, it might be assumed that the further step—namely, the merging of these phenomena within the same deficiency ambit—should be easy. We, indeed, began our investigations on this aspect of the question in the hope that the possession of the therapeutic key to the abortion sequence would automatically enable us to unlock the major secret. In this we have been disappointed. At the same time, certain data which have emerged during these investigations have seemed to us worthy of being placed upon record, especially as they relate to observations that can only be adequately tested on a larger scale than is generally possible in a single clinic. These observations can conveniently be discussed under four headings.

1. Influence of Prolactin and Progesterone on Confirmed Cases of Toxaemia

Over a period of about five years (since the discovery of the efficacy of prolactin and progesterone in abortion) we have, at different times and as the clinical potency of the commercial preparations improved, exhibited urinary prolactin or progestin preparations, as also vitamin E concentrates, to a considerable number of cases of established toxaemia. The results of these experimental trials have been almost uniformly negative. Except that in a few

instances of previously persisting hypertension we have noted a maintained lowering of the blood pressure, and that in several cases severe headache and visual disturbance exhibiting the usual toxic character disappeared at once after the administration of urinary prolan, we have been unable to arrest or control confirmed and aggravated cases. In the majority of instances there has been no effect on the hypertension and in none has the degree of albuminuria been appreciably lessened.

It is of course conceivable that, as in the habitual abortion of women and the blighted pregnancies of the lower animal, failure may be attributable to the fact that, unless commenced before the critical stage in placentation, the damage may be irrecoverable. This view would necessarily imply that where toxæmia occurs in the later months the causal factor from which it springs has in general operated during the early months, and that an interval clinically non-toxaemic separates the two events. The observations of Henry (1936) may, however, possess some relevance in this connexion. From a retrospective study of a large group of toxæmic patients this worker claims that in a high proportion evidence of the toxæmic process in the shape of a steadily mounting blood pressure may be discovered from as early as the fourth month. While they do not necessarily conflict with this view there is especial interest attached to the claims made by Shute (1937) that cases of premature separation of the placenta, even in the later months, can be successfully treated with vitamin E. This observation has an added interest on account of the close clinical relation known to exist between this condition and the toxæmic phenomena.

A factor which has militated seriously against the institution of an adequate testing of the preventive possibilities of the new therapy has been the paucity of material which our present management of toxæmia necessarily implies. It is obvious that the most suitable clinical material for such a purpose is the woman in whom, as we have shown in previous communications, the recurrence of toxæmia in two or more successive pregnancies enables us to infer an almost 100 per cent. risk in any succeeding gestation. But this has been just the class of case in which, with our existing knowledge, we have in general felt constrained to urge limitation by means of sterilization or, failing that, by contraception. This has left for experimental purposes a small group which are set out in Table IV, where, despite previous toxæmic stillbirths or a recurring series of alternating non-toxaemic and toxæmic pregnancies, the patient has insisted upon making a further attempt, during which the opportunity for the institution of early therapy has become possible. The results are suggestive, especially when we have regard to such apparently hopeless clinical prospects as are represented by Cases 1, 6, 7, and 8 (Table IV). Cases 1 to 8 further raise the question as to how far early commencement of the therapy may have succeeded in preventing or in controlling the toxæmic manifestations destined to develop in the later months and, in this way, to enable the gestation to be carried in safety to the birth of a living child.

2. Unmasking of Toxaemic Taint in a Pregnancy Successfully Carried to the Later Months

We have shown (Table I) that women with a history of repeated abortion seem to be exposed to a special risk of toxæmia in a pregnancy which extends into the later months. Similarly, in a case under treatment because of a history of repeated abortion, the successful carrying of the pregnancy to the last trimester by means of the substitution therapy may unmask the toxæmic taint (Cases 2,

5, 7, and 8, Table IV). This may imply that the factor making for toxæmia is identical with that responsible for abortion, and that, whilst the latter has been prevented, there has been left behind damage sufficient to initiate a toxæmia at a later date. It is clear that considerable evidence on this subject is required before we can speak with certainty. In the present state of our knowledge it is impossible to deny either that the previous abortions and the toxæmia may arise from one and the same source—a source other than that under consideration—or, alternatively, that the toxæmia has an entirely independent origin appearing merely because the pregnancy has been steered into the later and more vulnerable stage. That this unmasking phenomenon is by no means infrequent is demonstrated by the fact that we have recently obtained records from obstetrical colleagues of four further cases.

TABLE V.—*Toxaemia and Negative Friedman Test*

Case No.	Age	Previous Pregnancies	Present Pregnancy		
			Pregnancy Test	Toxaemia	Result to Child
1 (11357)	22	Nil	Friedman— 35 weeks	B.P. 170/105	Induction at 35 weeks Alive and well
2 (11425)	34	Nil	Friedman— 17 weeks	B.P. 158/98 Severe headaches	Progressing at 20 weeks
3 (11321)	26	(1) 8 mths. Died 28 hrs. (2) 7 mths. Died 8 hrs.	Friedman— 27 weeks	Headaches. Visual disturbance	Progressing at 33rd week Toxaemic symptoms subsided

3. The Gonadotropic Pregnancy Test in Toxaemic Cases

In two recent cases of toxæmia (Table V, Case 1, thirty-five weeks' pregnancy; and Case 2, seventeen weeks' pregnancy) the Friedman test, carried out to determine the question of foetal survival, was negative although subsequently the foetus was found to be alive. In Case 3 (Table V), that of a woman with a history of two previous premature children that died shortly after birth, the Friedman test was negative at the twenty-seventh week of the third pregnancy in association with mild toxæmic symptoms. On the other hand, in one woman (Case 7, Table IV) who had a previous history of three dead children born at full term, and who during her fourth pregnancy had long-continued ante-partum bleeding with some mild toxæmic symptoms, the Friedman test was positive at the twenty-eighth week. In a further case (Case 2, Table IV), with a previous history of two abortions, the Aschheim-Zondek test was positive at the third month, while toxæmia developed at the thirty-ninth week. No test was made at this later date. The negative findings in the three first cases quoted possess a special interest in view of the observations of Smith and Smith (1935), who claim that late pregnancy toxæmia is associated with an increased output of gonadotropic hormone.

4. Breaking of the Chain

Where there has been an unbroken habitual abortion-stillbirth sequence in which toxæmia features, the *breaking of the chain of disaster* under treatment and the birth of a live child is one of the most suggestive findings (Cases 1 and 6, Table IV).

The fuller records of some of the cases epitomized in the tables are instructive:

Case 1 (Table IV), aged 37, had suffered from severe and progressive toxæmia during the two preceding pregnancies,

the first ending in a stillbirth after artificial induction at the seventh month, the second ending spontaneously at the seventh month in the birth of a child which lived two days. She had been warned against further pregnancies. Disregarding this, she was first seen by me at the fifth month of her third pregnancy, when her health was good. The Aschheim-Zondek test was positive. She was placed on prolan therapy and carried to the thirty-seventh week, when the blood pressure began to rise (140/90) and a trace of albumin appeared in the urine. Induction at the thirty-eighth week resulted in the birth of a healthy child, which survived.

Case 5 (Table IV), aged 40, had a history of sound health apart from three previous abortions between the third and fifth months. She suffered from hyperemesis during the third month of her fourth pregnancy, for which hospital treatment was required. At the fourth month there was some vaginal bleeding. Under prolan treatment the pregnancy progressed satisfactorily till the thirty-eighth week, when albuminuria (0.05 per cent.) appeared with moderate hypertension (145/90). She was delivered at full term of a strong infant.

Case 6 (Table IV), aged 36, had had six obstetric disasters before being seen by the writer. Two abortions each at the second month were followed by a third pregnancy, in which there was very severe toxic hyperemesis, ending in a four-months abortion. The fourth pregnancy ended at the seventh month in a stillbirth after very grave toxæmic manifestations associated with coma. The fifth pregnancy ended in a three-months abortion, and the sixth with placenta prævia at the fifth month. Between the fifth and sixth pregnancies she was examined by a London obstetrician, who found her in the enjoyment of sound health. The writer first saw her after the sixth disaster when, apart from some septic teeth and mildly inflamed tonsils, which were removed, she was found to be healthy. A full investigation revealed no evidence of renal disorder. Though I made careful observation during a seventh pregnancy the membranes ruptured spontaneously at the sixth month, and four days later a macerated infant was delivered. There was no evidence of toxæmia. Despite this disastrous record the patient persisted, and under prolan therapy gave birth to a live child at full term after an uneventful eighth gestation. The statement regarding this last pregnancy we have received from the medical attendant of the patient.

Case 7 (Table IV), aged 23, had had three previous deliveries, all at full term. The first child was stillborn, the second lived a few hours, and the third one week. No cause was given for the death of the infants. She was first seen at the ante-natal clinic at the twenty-seventh week of her fourth pregnancy with a history of what she described as a more or less regular monthly loss of blood from the vagina lasting for two days on each occasion and continuing from the second to the eighth month. There was occasional abdominal pain and nausea, and vomiting had been present daily throughout. The Friedman test was positive. She was placed upon prolan therapy and, apart from a transient albuminuria and a slight rise of blood pressure (diastolic 90 mm. Hg.) she went to term and was delivered of a child which was strong and thrived well.

Diet and Fertility

The gradual emergence of the specific significance of dietetic factors in relation to fertility necessarily raises questions the importance of which extends beyond the range of the problems that beset the clinician. For it is obvious that, in so far as deficiency in these elements becomes increasingly identified with the factors responsible for abortion, it assumes a place of first-rate importance in the national economy. At the present moment it is impossible to state with any certainty the incidence of abortion which falls into this category. We may, however, safely assume that it constitutes a considerable proportion of "spontaneous" cases, and that it therefore must receive special attention in any future study of the factors which influence the national birth rate. The reorientation of our outlook on the bearing of diet on racial fertility which the

recent discoveries necessarily imply must awaken a new interest in the study of these problems and, more especially, as to the degree in which changes in the diet of the country have contributed to the steady decline in the birth rate during the past seventy years.

Summary

The evidence which has become available within recent years is consistent with the view that an important cause of the habitual abortion-stillbirth syndrome, which has baffled the clinician in the past, is a disturbance in the metabolism of pregnancy, in which a deficiency of vitamin E is involved. The evidence further raises the question as to the part which vitamin E plays in the prolan-progesterone mechanism of pregnancy.

The clinical applications of the results of recent research are simple and impressive.

In this communication some evidence is adduced for the view that the above considerations may likewise supply us with the missing *x* factor which we have previously postulated to explain the non-toxæmic recurrence of abortion, stillbirth, and accidental hæmorrhage in women who are subject to eclampsia and pre-eclampsia. This evidence is consistent with the view that major degrees of deficiency tend to interruption of pregnancy in the early months without toxæmic manifestations, whereas if the deficiency is less marked the pregnancy is capable of progressing to the later months with a consequent risk of toxæmia.

The evidence reviewed in this communication raises the question as to the part played by diet in racial fertility and more especially as to how far changes in the consumption of essential dietetic elements may have contributed to the declining birth rate.

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The International Union of Local Authorities will hold a conference in Paris from July 5 to 11 under the patronage of the French Government. The two main questions for discussion are: (1) pollution of the air by smoke, gases, and dust; and (2) the supply of milk and the regulations necessary for public health. Dr. Thomas Orr, M.O.H. for Ealing, is the British reporter on the question of milk, and Dr. J. Johnstone Jervis, M.O.H. for Leeds, on atmospheric pollution. The sessions on these subjects will be held at the "Maison de la Chimie," 28, Rue St. Dominique. The secretary for Great Britain is Mr. T. A. Avis, 26, Abingdon Street, Westminster, S.W.1.