HUMAN DECIDUAL SPIRAL ARTERIAL STUDIES

PART VIII. THE AETIOLOGICAL RELATIONSHIP BETWEEN TOXAEMIA-HYPERTENSION OF PREGNANCY AND SPIRAL ARTERIAL PLACENTAL PATHOLOGY

A STATISTICAL STUDY

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There is a definite association between certain spiral arterial and placental lesions and the clinical features presented by the groups of patients in whom such lesions were found.[30] The likely nature of these associations, however, remained obscure.

Opinions are much divided about the possible aetiological relationships which may exist between pre-eclamptic toxaemia-hypertension and placental ischaemia or infarction.[1-8,10,12,13,16-18,20,22,31,33-42] Most authors believe that some important association exists between pre-eclamptic toxaemia-hypertension and abruptio placentae.[41,42,6,11,32,9,14] As yet there is no agreement on the aetiological relationship between placental infarction and abruptio.[41,42,6,15,14,23,21] The consensus of present-day opinion, which has been confirmed by a number of authors,[24-29] is that placental ischaemia and infarction are mediated by an interference with the maternal placental circulation.

From these introductory notes it is evident that the aetiological relationship between pre-eclamptic toxaemia-hypertension on the one hand, and spiral arterial-placental pathology and accidental haemorrhage on the other, requires further attention. As placental infarction and abruptio placentae are secondary to spiral arterial pathology, the aetiological relationships of the latter rather than the former abnormalities should be examined first.

Is hypertension or spiral arterial pathology the primary factor? Does hypertension result in spiral arterial damage and placental infarction, or is spiral arterial pathology and its sequelae, placental ischaemia and infarction, primary — resulting in the release of toxins which cause the toxaemia; or are both hypertension and spiral arterial pathology caused by another factor, so that in some cases only hypertension is present, in others only spiral arterial damage, and in a third group a combination of these? What are the pathological and the clinical characteristics of such groups?

The following theory was considered to hold the key to the possible solution of these questions: If there is a group of patients in whom spiral arterioles are severely damaged, yet who have had no symptoms or signs of toxaemia, then, in the first place, it is unlikely that hypertension is a necessary prerequisite to spiral arterial damage and, secondly (the reverse), spiral arterial damage and its sequelae are probably not the causes of toxaemia. To put this argument in a different way: if a group of patients have essentially normal spiral arterioles yet hypertension was present, then, firstly, the hypertension is unlikely to have influenced their state of health to any recognizable extent and, secondly, since the spiral arterioles were not damaged beyond physiological limits, it is most unlikely that the hypertensive factor was derived from them.

Materials and Methods

These have been described and discussed in detail elsewhere.[24,25,28,30] In the present study the placentas from 1,000 consecutive deliveries were examined from a clinical, macroscopic, colposcopic and histological angle. For the final analyses the 885 cases with single pregnancies, in whom spiral arterioles were found histologically, were selected. The individual data were first correlated by means of International Business Machines' (IBM) 1401 electronic computer. The data, which were derived from the computer analyses, were presented to Schumann* for a completely independent expert statistical appraisal. The results so obtained were then subjected to clinical interpretation. Four groups were selected to test the above-mentioned theory [Table I, Groups (1), (2), (3) and (4)]. The characteristics of these groups were compared with those of the entire sample of 885 (overall) cases. Groups (3) and (4) were then further analysed (Table II).

RESULTS

The results are summarized in Tables I and II.

Table I

Group (1) is a normal group in all respects. In group (2) the spiral arterioles are essentially normal although a diastolic blood pressure of over 100 mm.Hg had been recorded on one or more occasions, and a raised systolic blood pressure and

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TABLE I. SPECIFIC BLOOD PRESSURE PLUS SPIRAL ARTERIAL GROUPINGS IN RELATION TO CLINICAL FEATURES

Clinico-pathological groups	*Number of cases in group*	*Race* (*European, Coloured, Malay, Bantu*)	*Age* (*Mean, years*)	*Gravida* (*Mean*)	*Accidental haemorrhage* (% *abruptio*, % *unclassified*)	*Eclampsia* (%)	*Duration of observation* (*Mean, weeks*)	*Onset of labour* (% *LUSCS* % *ARM*)	*Method of delivery* (*Spontaneous, forceps, Caesarean, manipulation*)	*Duration of pregnancy at delivery* (*Mean, weeks*)
(1) Normal and mildly abnormal spiral arterioles	458		25·30	3·02	1·75 1·53	0·66	11·76	0·44 2·18		39·25
Diastolic blood pressure never recorded above 89 mm.Hg		NS	1%	NS	NS	NS	10%	10%	NS	NS
(2) Normal and mildly abnormal spiral arterioles	98		27·60	3·68	1·02 1·02	2·04	10·04	1·02 20·41		38·78
Diastolic blood pressure of 100 mm.Hg or above recorded on one or more occasion		NS	5%	NS	NS	NS	NS	10%	NS	NS
(3) Severely abnormal spiral arterioles	29		26·25	4·38	0·00 0·00	0·00	11·17	0·00 0·00		38·54
Diastolic blood pressure never recorded above 89 mm.Hg .. .. + further analyses of this group (Table II)		NS	NS	10%	NS	NS	NS	NS	NS	NS
(4) Severely abnormal spiral arterioles	41		28·25	3·59	21·96 0·00	4·88	5·88	7·32 53·66		36·32
Diastolic blood pressure of 100 mm.Hg or above recorded on one or more occasions + further analyses of this group (Table II)		NS	5%	NS	10+%	NS	1%	1%	NS	1%
Overall	885	23·62 54·69 5·99 15·71	26·10	3·24	2·37 1·58	0·79	11·20	1·36 7·12	86·78 6·55 6·21 0·45	39·05

Clinico-pathological groups	*Outcome of child* (% *stillbirth* % *neonatal death*)	*Weight of child* (*Mean, pounds*)	*Placental weight* (*Mean, ounces*)	*Placental volume* (*Mean, millilitre*)	*Colposcopic evaluation of spiral arterioles* (% *abnormal*)	*Systolic blood pressure* (*Mean, mm.Hg*)	*Diastolic blood pressure* (*Mean. mm.Hg*)	*Albuminuria* (*Mean, 0—4+*)	*Oedema* (*Mean, 0—4+*)
(1) Normal and mildly abnormal spiral arterioles	1·75 0·66	6·45	16·13	490	7·86	121·18		0·07	0·05
Diastolic blood pressure never recorded above 89 mm.Hg	NS	NS	NS	NS	1%	1%		1%	1%
(2) Normal and mildly abnormal spiral arterioles	3·06 0·00	6·36	16·59	504	10·20	160·20		0·70	0·52
Diastolic blood pressure of 100 mm.Hg or above .. .. recorded on one or more occasion	NS	NS	NS	NS	10+%	1%		1%	1%
(3) Severely abnormal spiral arterioles ..	3·45 0·00	5·90	15·28	460	65·52	123·10		0·25	0·00
Diastolic blood pressure never recorded above 89 mm.Hg .. .. .. + further analyses of this group	NS	NS	NS	NS	1%	10+%		NS	NS
(4) Severely abnormal spiral arterioles ..	29·27 4·88	4·90	12·88	384	95·12	171·50		2·07	1·28
Diastolic blood pressure of 100 mm.Hg or above .. .. recorded on one or more occasions + further analyses of this group	1%	1%	1%	1%	1%	1%		1%	1%
Overall	3·16 0·79	6·38	15·98	486	16·61	132·43	87·45	0·28	0·21

EXPLANATORY NOTES TO TABLE I

1. Spiral arterial health or disease in terms of which Groups (1), (2), (3) and (4) were selected, has been diagnosed histologically.
2. The 'duration of observation' here recorded was the duration of attendance at the University Maternity Institutions.
3. LUSCS = Lower uterine segment Caesarean section. ARM = Artificial rupture of membranes.
4. 'Method of delivery' was either spontaneous, by forceps, Caesarean section, or other manipulations.
5. The cases recorded as 'neonatal deaths' were those foetal deaths which occurred within 24 hours of delivery. In association with the stillbirths they are the group with 'immediate foetal loss' as in Table II .
6. NS—The value obtained at a specific analysis does not differ to a statistically significant level from that of the entire sample (885) overall. 1%, 5%, 10% and 10+% indicate the statistically significant levels at which the values obtained at specific analyses differ from that of the entire sample.

albuminuria are present in statistically significant proportions. In spite of the fact that no signs of toxaemia were ever detected in group (3) (which is confirmed by the absence of any inductions in this group), they had severe spiral arterial damage. This fact is also reflected in the colposcopic figure. Despite the severe arterial damage in this group, the low rate of accidental haemorrhage, eclampsia and foetal loss recorded in groups (1) and (2) are maintained.

In group (4), however, where a raised blood pressure plus severe spiral arterial disease is present, the difference in nearly all the clinical features is most striking, including the fact that spiral arterial abnormalities could be diagnosed with the colposcope in 95% of the cases. There was no difference in the race distribution of the various groups.

A closer scrutiny of the non-hypertensive and the hypertensive-albuminuric severe spiral arteriolar disease groups is next indicated. In order to throw light on the question of which of the severe arterial lesions are responsible for the high rate of accidental haemorrhages and foetal loss in the hypertensive group, these two groups were analysed for pathological features and clinical results.

Table II

In Table II a detailed analysis of the groups with severe spiral arterial pathology is given: (*a*) With a low blood pressure, and (*b*) with a raised blood pressure.

The information in the table is arranged in such a way that data about the lesions least associated with toxaemic signs are followed by data about the more severe types: first the spiral arterioles, then colposcopic assessment of spiral arterioles, the general assessment of intraplacental lesions, individual intraplacental lesions, the association of the particular groups with accidental haemorrhage (as diagnosed pathologically and clinically), and immediate foetal loss.

Though the types of lesions in the low blood pressure group are similar to those in the high blood pressure group, an unmistakably different trend in the virulence of the lesions in the two groups is noted. There is a progressively increasing incidence of the more severe type of lesions in group (*b*). This is particularly well illustrated in the group with sudden thrombosis of spiral arterioles, which is especially prone to result in intraplacental lesions of more than 1 cm. in diameter, abruptio placentae, red infarcts and also white infarcts. In addition, nearly all the spiral arterioles could be recognized with the colposcope as being abnormal. There are striking differences in the incidence of diagnosis of accidental haemorrhage at placental examination, the clinical history of accidental haemorrhage, and the immediate foetal loss.

If an analysis of the patients who (clinically) had accidental haemorrhage is made. Table II (*b*)(1), the importance of sudden complete thrombosis and of rupture and disintegration of spiral arterioles becomes quite obvious: white and red infarcts were produced, as well as evidence of accidental haemorrhage at placental examination, and the association of these lesions with foetal loss is strikingly demonstrated. In only the two mild cases with accidental haemorrhage, was its occurrence not suspected at placental examination.

Analysis of the 14 cases with immediate foetal loss, Table II (*b*) (2), re-emphasizes the importance of severe spiral arterial pathology (in the form of sudden complete thrombosis, and to a lesser extent, disintegration with white and redinfarct formation and accidental haemorrhage) in producing foetal loss.

TABLE II. DETAILED ANALYSIS OF THE GROUPS WITH SEVERE SPIRAL ARTERIAL PATHOLOGY—WITH A LOW BLOOD PRESSURE AND WITH A RAISED BLOOD PRESSURE

Clinico-pathological groups	*Total number of cases in group*	*Mild intimal fibroblastic response of spiral arterioles*	*Mild intimal fibrin deposits in spiral arterioles*	*Layered partial thrombosis of spiral arterioles*	*Layered complete thrombosis of spiral arterioles*	*Fibrinoid necrosis of spiral arterioles*	*Foam cell infiltration of spiral arterioles*	*Sudden complete thrombosis of spiral arterioles*	*Disintegration or rupture of spiral arterioles*	*Colposcopic assessment of spiral arterioles number diagnosed as abnormal*
(*a*) *Severely abnormal spiral arterioles .. .. (Diastolic blood pressure never above 89 mm.Hg)	29	27 (93·10%)	26 (89·65%)	11 (37·93%)	7 (24·14%)	15 (51·72%)	11 (37·93%)	15 (51·72%)	6 (20·69%)	19 (65·52%)
(*b*) †Severely abnormal spiral arterioles .. .. (Diastolic blood pressure 100 mm.Hg and over, once or more) ..	41	36 (87·80%)	39 (95·12)	12 (29·27%)	8 (19·51%)	25 (60·98%)	18 (43·90%)	31 (75·61%)	23 (56·10%)	39 (95·12%)
(1) Analyses of the cases with accidental haemorrhage in this group	9	8 (88·89%)	8 (88·89%)	2 (22·22%)	1 (11·11%)	2 (22·22%)	0 (0·00%)	8 (88·89%)	5 (55·55%)	8 (88·89%)
(2) Analyses of the cases with immediate foetal loss in this group	14	11 (78·57%)	13 (92·86%)	4 (28·57%)	3 (21·43%)	6 (42·86%)	2 (14·29%)	13 (92·86%)	8 (57·14%)	13 (92·86%)

Clinico-pathological groups	*Intraplacental lesions less than 1 cm. diameter*	*Intraplacent lesions more than 1 cm. diameter*	*Intraplacental fibrin deposits and thrombi*	*Intraplacental white infarcts*	*Intraplacental red infarcts*	*Diagnosis of accidental haemorrhage at placental examination*	*History of accidental haemorrhage*	*Foetal loss immediate: Stillbirth*	*Foetal loss immediate: Neonatal death*
(*a*) *Severely abnormal spiral arterioles .. (Diastolic blood pressure never above 89 mm.Hg)	9 (31·03%)	4 (13·79%)	9 (31·03%)	15 (51·72%)	3 (10·34%)	0 —	0 —	1 (3·45%)	0 —
(*b*) †Severely abnormal spiral arterioles .. (Diastolic blood pressure 100 mm.Hg and over, once or more)	16 (39·02%)	15 (36·59%)	8 (19·51%)	24 (58·54%)	17 (41·46%)	12 (29·27%)	9 (21·95%)	12 (29·27%)	2 (4·88%)
(1) Analyses of the cases with accidental haemorrhage in this group	5 (55·55%)	4 (44·44%)	2 (22·22%)	7 (77·78%)	4 (44·44%)	7 (77·78%)	9 (100·00%)	9 (100·00%)	0 (0·00%)
(2) Analyses of the cases with immediate foetal loss in this group	6 (42·86%)	7 (50·00%)	3 (21·43%)	8 (57·14%)	8 (57·14%)	8 (57·14%)	9 (64·29%)	12 (85·71%)	2 (14·29%)

* (*a*) Of the 29 cases only 1 (3·45%) had both white and red intraplacental infarcts.
† (*b*) Of the 41 cases 11 (26·83%) had both white and red intraplacental infarcts.
(1) Of the 9 cases 3 (33·33%) had both white and red intraplacental infarcts.
Of the 14 cases 4 (28·57%) had both white and red intraplacental infarcts.

SUMMARY AND CONCLUSIONS

Table I

Unless very high, raised blood pressure is probably not the primary cause of spiral arterial damage.

When hypertension is present, but is unassociated with severe spiral arterial pathology, the prognosis is good.

Severe spiral arterial damage may be found unassociated with hypertension. The presence of such pathology may not be recognized clinically in any way.

It is therefore probably not the spiral arterial abnormalities or their sequelae which result in toxaemia.

If severe spiral arterial pathology plus hypertension is present, the clinical results are catastrophic. In other words, in a certain group of cases a hypertensive factor is released, apparently with little damaging effect on spiral arterioles or clinically; in another group a damaging factor to spiral arterioles is produced, also with little clinical effects. In a third group both a hypertensive and a vascular damaging factor is released – with catastrophic results. Note also that:

1. In addition to hypertension, the amount of albuminuria may serve as a very sensitive guide to spiral arterial damage, probably because the renal vessels are similarly affected.

2. An association between hypertension and advancing age is reflected in groups (1) and (2) – normal and mildly abnormal spiral arterioles without and with a raised blood pressure. This association may be due to an element of essential hypertension having appeared in the older age group. A similar trend is noted in groups (3) and (4). It seems possible that this hypertensive element in the older age group may be partly responsible for the aggravation of already severely damaged spiral arterioles, thus resulting in the adverse placental pathological and clinical results which are noted in group (4). A suspicion of this nature has already been aroused earlier,[30-table iv] when a trend was noted suggesting that in patients with more severe degrees of abruptio placentae advancing age was an important factor.

Table II

Two groups of severe spiral arterial pathology exist. The group which occurs in association with a normal blood pressure is relatively benign, both in its production of placental pathology and its clinical results. The group which is associated with a raised blood pressure is much more virulent in nature, both as far as the placental lesions and clinical results are concerned. The spiral arterial lesion, which stands out as the prime lesion in both the accidental haemorrhage and stillbirth analyses, is *sudden complete thrombosis of spiral arterioles in association with a raised blood pressure and albuminuria.* It is this lesion which is mainly responsible for pattern A red infarcts and abruptio placentae.

This analysis strongly suggests that there is a spiral arterial damaging factor unassociated with recognizable toxaemia, but if this factor is present in association with hypertension, then the spiral arterial damage becomes much aggravated, with catastrophic results to the placenta, the mother and the foetus. The question is where and how to look for these hypertensive and vascular damaging factors.

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