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Modern theories of the etiology of premature separation of the placenta

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The possible etiology of premature separation of the normally implanted placenta has been speculated upon and argued about since the condition was first recognized and differentiated from placenta previa. The ideas propounded have been nearly as numerous as the observers of the condition. There has been very little direct evidence obtained, either pathological or experimental, which will even begin to conclusively answer the question in all cases. Much of the evidence of possible causes comes indirectly from comparative statistical study of series of cases. These various series are very hard to evaluate and compare however, because of great variations in size of series, differences in diagnosis and ideas of what constitutes premature separations, differences in types of patients, and in complicating conditions. There is no agreement in the various series concerning the relationship of the condition to trauma, uterine disease, toxemia or complicating diseases such as nephritis.

All this variability and uncertainty would seem to point to involvement of several factors in the etiology of the condition. The differences in clinical symptoms and the ultimate outcome of the condition also suggests more

than one cause. There could, of course, be one basic cause with several predisposing causes.

It is the purpose of this paper to present the various theories of the etiology of premature separation of the placenta that are held at the present time, and to discuss the possibility of a basic cause for the clinical types which show widely varying symptoms and course.

CLASSIFICATION

Kellog (19) presented a simple classification of premature separation of the placenta based on a pathologic approach. This classification seems to be satisfactory and will be followed in this discussion. It is as follows:

I. Pathologic separation of the normally implanted placenta. In these cases there are no clinical manifestations. This is a frequent finding in the study of stillbirth placentae.

II. Placental developmental abnormalities resulting in premature separation of the normally implanted placenta. An example of this is placenta circumvallata.

III. Traumatic separation of the normally implanted placenta. In these cases the placenta is normal.

IV. Non-toxic separation of the normally implanted placenta. In these cases the "crystallization" of the support between the decidua and tropho-

blast on a senile degenerative basis accounts for the separation.

V. Toxic separation of the normally implanted placenta. This is the largest and most important group. It is also the group with the highest fetal and maternal mortality rates.

PATHOLOGIC SEPARATION

This is a very small group as compared with the large number of cases in which no definite disease process can be demonstrated. In this class is included those cases of separation caused by syphilis and by non-specific infections of the endometrium and placenta. The latter is very rarely seen to cause the condition. At one time syphilis played a more prominent role in placental pathology than it does now. With the advent of mass serologies and modern methods of treatment it has fallen to a minor role, especially as an etiological agent in premature separation. It is possible that it never did play too prominent a part in the causation of the condition but since its major feature is placental infarction and since a placenta, separated from any cause may show infarcts, the reason for confusion is obvious.

This group is unimportant as far as premature separation of the placenta is concerned and in any case in which it is the cause, the serology and study of placental pathology would make the diagnosis obvious.

The infarcts associated with toxic separation are not included in this group but are discussed under that heading.

PLACENTAL DEVELOPMENTAL ABNORMALITIES

This group is so rare a cause of premature separation that it is often not considered. One reason for this rarity is that these abnormal placentae may be incompatible with development and become detached early so that they are abortions rather than premature separations. They are probably of slight importance clinically unless there occurs a concealed hemorrhage. In this case a toxic sequence might ensue as explained in a later section.

TRAUMATIC SEPARATION

External trauma was considered by older writers to play the leading etiologic role. This was first suggested by Rigby (7) and carried on by others. In his series of 200 cases, Holmes (17) believed trauma to be the cause in 33.5%. Since that time, however, in all reports external trauma has played only a minor part. Harrer (7) reported trauma in 5.9%, Polak (7) in 18.7%, Davis and McGee (7) in 1.8%. Many authors have reported series in which trauma played no part whatever.

The figures given above cannot be strictly compared because of great difference in size of series, different social strata etc., but they do serve to show that since the

turn of the century, trauma has fallen to a minor place in the consideration of causes of premature separation of the placenta. This is probably largely due to the fact that other more prominent possible causes have been recognized, but it may also be due to the fact that in the general population pregnant women are subject to much less opportunity for trauma now than they were a century ago.

Internal trauma, resulting from manipulation or operative procedure, is more important than external trauma; but it too is a minor factor when compared with the many cases occurring suddenly with no trauma either external or internal, or no other obvious cause for that matter.

Another cause to be considered under internal trauma is a short cord which causes undue traction on the placenta. This is also an uncommon cause. The only definite figures I found were from a series of 164 cases reported by Davis and McGee (7) in which they found an incidence of 2.4%. This possible cause is hard to evaluate because of the difficulty of determining what a "short cord" really is. A cord of normal length, if it became entangled with the fetal extremities might have the same effect as an abnormally short cord.

Another factor which may be of considerable importance was put forth by Bartholomew and Kracke (1) to account for some types of placental infarcts. This factor is trauma

to the placenta from the vigorous fetal movements during the last weeks of pregnancy. This trauma might cause rupture of small vessels with resultant extravasation of blood into the tissues. The significance of this will be discussed later.

NON-TOXIC SEPARATION

Hertig (11) believes that he has microscopic pathologic evidence that there are two types of changes in placentae which have prematurely separated. One of these is on a strictly senile degenerative basis and the other is due to some unknown factor associated with toxemia. The latter will be discussed under toxic separation.

The pathologic picture as he describes it is a "moth eaten" or cystic degenerative process beginning in the trophoblastic layer of either the placental septa or site. The vascular supply of the placenta depends on the integrity of the placental site rather than on any intrinsic strength of the vessels themselves so any dissolution of the site will result in rupture of the vessels with hematoma formation and placental separation.

This type of basic mechanism of separation does not mean that all these cases with this microscopic picture will not have associated toxic symptoms. As Young (25) has pointed out, there are cases in which the bleeding is primary and followed by the toxic symptoms. If the bleed-

ing is concealed there is especially likely to be secondary toxic symptoms with azotemia, oliguria and a general picture resembling "crush syndrome". Such a case would undoubtedly be classed clinically as belonging to the toxic type of separation, whereas the basic factor starting the whole process is different.

A good percentage of most series do not show any signs of toxemia. For instance, Young's series of 79 cases showed 74.7% in this group. While this does not mean that all these cases are due to the primary pathologic change described above, it is suggestive that this might be a prominent factor in a good number of cases.

TOXIC SEPARATION

It has been observed by many authors that there is frequently evidences of toxemia in cases of premature separation and that some cases of toxemia may suddenly develop premature separation. From the work of Winter (7) until the present time, this relationship has been noted in most series of cases. This relationship would seem to point to some single basic factor in the development of both toxemia and premature separation.

However, Davis and McGee (7) did not believe this to be necessarily true. They pointed out that while there is a significant relationship between toxemia and premature separation, the incidence of premature separation with true

eclampsia is very low. They also found a low incidence of chronic nephritis associated with premature separation. In their series of 164 cases of premature separation, they found an incidence of toxemia in 56.6%, chronic nephritis in 9.6%, and of eclampsia in .6%.

It appears then that there is some common denominator in the etiology of both toxemia and the majority of cases of premature separation but as yet no one has been successful in proving definitely what this factor is.

Some of the first experimental work along this line was done by Hofbauer (12). He injected histamine into pregnant guinea pigs and observed that the resulting condition was very similar to premature separation occurring in women. The phenomena he observed were shock, spasm of the uterus, separation of the placenta, engorgement of the vessels of the uterus and broad ligament, hemorrhage into various organs, edema of the uterine wall and degenerative changes in the liver and kidneys. In dogs after similar treatment he found changes which greatly resembled those found in women who died of eclampsia, i.e., peripheral necrosis of the liver associated with formation of thrombi and bile stasis, and in the kidney, degenerative changes of the epithelium of the convoluted tubules. He concluded that the mechanism responsible in both instances rests on the action of some endothelial toxin which renders the capillaries more permeable

to the body fluids.

Browne (4) produced premature separation and placental infarction in experimental animals by injection of sodium oxalate or uranium nitrate, which produced a chronic nephritis, and then injecting bacillus pyocyaneus. He believed the separation in this case to be due to the inability of the kidneys to excrete the poisons from the circulation.

A great deal of work has been done to try to relate various types of placental infarcts with toxemia and premature separation. The various organs of the endocrine system have been shown to be involved in the process. These various possible etiological factors will be discussed in detail in the next section.

DISCUSSION

The mechanics of premature separation are similar to those of the third stage of labor. There is a retro-placental hematoma formed, which may dissect the placenta away from the uterine wall or if situated near the margin may cause external bleeding with little actual separation. The answer to the problem of etiology lies then, in whatever causes the bleeding to begin.

As mentioned previously, trauma is undoubtedly involved in some cases but these are in the minority. Holmes (17) thought that trauma was perhaps only contributory, the basic cause being some pathologic condition in the maternal por-

tion of the placenta.

The majority of cases then are to be found in the last two groups of Kellog's classification. The most important of these, by far, are those of the moderate to severe toxemic group because it is these patients which show the high mortality rates. Most writers agree that this mortality is due to the toxemia rather than to the hemorrhage.

The division of non-toxic and toxic cases seems to be rather artificial because Young (25) has shown that the non-toxic cases have potentialities for becoming toxic if the hemorrhage is concealed or partly concealed. It appears then, that all cases of premature separation except traumatic are intimately linked in their etiology with toxemia and that even traumatic cases can become toxic if the bleeding is concealed. In fact, Bartholomew (3) believes that premature separation is simply one phase of toxemia and Hertig (11) describes it as "uterine eclampsia".

Many theories have for their basic theme, some vascular lesion in the placenta but the details from that point on are quite varied. McKelvey (20) describes a series of changes in the arterioles in the upper portion of the decidua basalis. These changes begin with replacement of the vessel wall and endothelium by a fibrinoid substance. There is gradual dilatation of the lumen and extension of the

fibrinoid substance causing an increase in the coiling of the vessel. All this leads to weakening of the vessel wall and rupture with varying degrees of hemorrhage. He describes these changes as occurring in the normal placenta. If a large enough vessel should rupture or for some reason the blood would not clot, premature separation would occur. He describes the maternal circulation in the placenta as an arteriovenous aneurysm because the arterioles and veins are connected by intervillous spaces and no capillaries. He believes that this predisposes in some way to the degenerative changes and infarcts seen in all placentae.

Hertig (11) describes two different types of degenerative lesions to explain non-toxic and toxic separations. His non-toxic type is a cystic degenerative process in the trophoblastic layer of the placental septa or site. This dissolution of the placental site causes rupture of venous sinuses and hemorrhage. As the marginal veins are usually affected, the hemorrhage is usually external. The toxic type of lesion, he believes, is a degeneration or arteriolitis of the arteriole wall which leads to a gradual obstruction of the lumen with thrombus formation. Hemorrhage and necrosis occur at the site of the obstruction, then some fibrinolytic enzyme is formed which causes the toxemia. This vascular change is probably a cholesterol-vascular change from deposits of cholesterol in the vessel wall.

Bartholomew (3) in comparing this with the same condition in the coronary arteries believes that the result would be thrombosis but not hemorrhage. At one time (1) he tried to show that there was a cholesterol-vascular change in the placenta due to a hypercholesterolemia in pregnancy and that the deposition might be increased by slight trauma to the arteries due to fetal movements. However, in his latest paper (3) he does not believe this to be the cause, because thromboses could not be found adjacent to cholesterol deposits at the sites of possible trauma to the fetal surface of the placenta.

While Williams (23), Young (25), Kellog (19) and Hertig (11) believe that the essential vascular interference is in the maternal circulation, Bartholomew et al (3) believe it to be on the fetal side. Bartholomew's latest theory involves the sphincters in the fetal collecting veins of the placenta described by Spanner (3). He believes that some spasmogenic influences may act upon them, causing stoppage of the circulation with thrombosis and infarction of the villi. The source of this spasmogenic influence is uncertain. He ventures that it might be pituitary or renal in origin.

Dieckmann (8) thinks that there must be an element of hypertension, either manifest or latent intensified by pregnancy, in addition to the vessel changes in order that

rupture and hemorrhage occur. He states that infarction and premature separation seem to be the same process, differing only in speed of occurrance and position of the obliterated vessel.

Another factor which several theories include is the occurrence of infarcts. Bartholomew is the greatest promoter of this also. In his latest series (3) he found hemorrhagic infarcts in all cases of premature separation, pre-eclampsia, and eclampsia. He believes the reason most observers do not find this to be consistently true is failure to properly fix the placenta before attempting to study it. Falkiner (10) is in agreement with these findings. Other authorities (21) believe that some cases of what Bartholomew calls hemorrhagic infarct may actually be hemorrhage into the tissue without necrosis.

Bartholomew classifies placental infarcts as anemic, acute hemorrhagic and subacute hemorrhagic. The first is due to obliterative endarteritis which gradually occludes fetal circulation to the tissues with resulting slow necrosis of the villi, inducing thrombosis of maternal blood in the sinuses with hyalinization and white infarct formation. This is in accord with Young (25) and Hertig's (11) view of infarct formation, except they believe that it starts on the maternal side. The hemorrhagic infarcts, he believes, are due to the phenomenon of spasmogenic influences mentioned

above. While Hertig and Kellog believe that the hemorrhage is primary, followed by infarct formation, Bartholomew believes he has pathologic evidence to prove that the infarct is primary followed by the hemorrhage which causes the separation.

The next logical step is to use the pathologic change--infarcts or concealed hemorrhage--to try to explain the frequently associated toxemia. There is a lot of variation clinically in the relation of the appearance of signs of toxemia and those of premature separation.

Young (25) believes that there is evidence that in most cases retroplacental bleeding is primary and that the degree of toxemia depends on the extent of the lesion. Bartholomew presents evidence that the hemorrhagic infarct is primary with resulting toxemia and retroplacental hemorrhage secondary. If the hemorrhage is not extensive enough to cause separation, only toxic symptoms will result. As stated before, he looks upon toxemia and separation as the same process. The actual factor from the infarct or hemorrhage causing the toxemia is much debated. A great many attractive theories of the probable toxin involved and its mode of formation have been advanced but so far no specific poison has been definitely incriminated. The basic idea is that some poison or poisons are absorbed into the maternal blood stream from the necrotic tissue. This poison is supposed to

cause the lesions found associated with premature separation and with toxemia.

Some investigators, such as Kellog (19), do not try to specify any actual chemical but identify the substance as a fibrinolytic enzyme. Others, Hofbauer (12), Browne (4) and Bartholomew (2) have, on experimental evidence, conjectured some specific poisons. The picture, which Hofbauer produced with histamine in guinea pigs and dogs, resembling toxic premature separation has already been mentioned. Bartholomew and Parker (2) believe that histamine might be a prominent factor in the so-called Couvelaire uterus.

Following the discovery of histaminease in the placenta (6), several authors (15) reported that there is always a high blood level of this enzyme in normal pregnancies. Cusmano (5) found the activity of the enzyme to be decreased in severe pre-eclampsia and markedly decreased in premature separation. He also found the blood level of histamine and histamine-like substances to be fifty times higher than normal in premature separation of the placenta.

Another piece of evidence in favor of histamine comes from the observation of Kapellar-Adler (18) that in the urine of normal pregnant women there is histidine present in measurable amounts but that in pre-eclampsia it disappears. The theory here is that histidine is changed to histamine by a tissue decarboxylase and the excess histamine causes the

symptoms and the pathology. However, histidine is normally changed to histamine by the liver in non-pregnant women so the mere formation of it by a different mechanism in the pregnant state does not appear to be the basic cause of the toxemia. The rate of formation might be a major factor or some substance similar to histamine but of greater potency might be formed; or there may be some mechanism for handling histamine in the non-pregnant state which is not operating in the pregnant state. The above evidence of a greatly decreased blood level of histaminase in premature separation is the only tangible evidence so far by which this might be explained.

Recently Hoffman (16), on the theory that histamine may play a part on toxemias, tried an antihistamine drug (pyribenzamine) in the treatment of 40 patients with signs of early toxemia. He showed definite improvement in all except three of them. His work is as yet unconfirmed. This is further evidence which points to histamine as a major factor involved.

Another poison advanced by Bartholomew and Parker (2) is guanidine. They believe it has more to do with eclampsia and histamine more to do with premature separation. The effects of guanidine poisoning are; disturbance of carbohydrate metabolism, fluctuation of blood sugar, increase in blood uric acid, amino acid and lactic acid, increase

in blood pressure, edema, renal damage and convulsions. Arginine is found in quite large amounts in placental tissue and they believe it to be a precursor of guanidine. There is no actual proof of this however.

Peptone is also mentioned as a possible poison involved. They believe the occurrance of the conditions of pre-eclampsia, eclampsia or premature separation depend on the number, size and location of the infarct, degree of blockage of the circulation and the rate of autolysis.

Young (25) and Kellog (19) have an intriging theory which seems to explain the lack of toxic symptoms in certain cases of separation, especially those with external hemorrhage. They believe the toxins are released from the autolysing retroplacental hematoma rather than an infarct and so if the blood is escaping no toxins are absorbed. In their cases of toxic separation they noticed a great similarity to the "crush syndrome" with renal failure and renal lesions. In this case the hemorrhage would have to occur from some of the causes already postulated and the toxemia come secondary from absorption of free hemoglobin and other toxic products of autolysis.

We have gone over the various factors but still the basic factor which might set off the whole process has not become tangible. Hypercholesterolemia due to changed metabolism in pregnancy might be a factor in the vascular change.

Histamine has been suggested as a cause of the picture of toxic premature separation, the increased histamine being due to a decreased blood level of histaminase, formation of histamine from necrotic tissue or some abnormal change of histidine to histamine; but the basic factor which might set such a chain of events in motion is not clear.

Hofbauer (14, 15) and others believe that perhaps the answer to this lies in some abnormality of the endocrine system. The remaining prominent theories of premature separation are built around this belief. Smith and Smith (22) found a close correlation between the clinical findings and a decreased estrogen and progesterone blood level in pre-eclampsia, and believed that the symptoms were alleviated (even though temporarily in some cases) by the administration of these hormones. Their conclusion was that the clinical manifestations of toxemia are the result of changed metabolism of the sex steroids involving a greatly increased rate of destruction. They offered no theory as to the exciting factor in this abnormal metabolism.

Hofbauer's present theory (15) is quite unique and while it is based partly upon the presence of increased amounts of histamine, its formation is explained in a different manner. He believes that there are syncytial buds which grow out from the villi into the maternal blood lakes, gradually detach themselves and finally dissolved in the

maternal blood stream. He has experimental evidence to show that these fragments stimulate the various ductless glands in the maternal system. These fragments are active, he thinks, by release of split-protein products--histamine-like substances. They also carry into the circulation substances which are stored in the placenta in large quantities, namely sex hormones and acetylcholine. The sex hormones cause a hyperplasia of the pituitary gland as shown experimentally by Berblinger and Vasquez-Lopez (15). The split-protein products are damaging to the maternal organs, primarily the liver, causing some degree of insufficiency. Normally, he postulates, there is an antagonistic action between acetylcholine and the vasopressor substances produced by the pituitary, thyroid and adrenals.

During pregnancy the additional amount of acetylcholine necessary to counteract the effects of the excess vasopressor secretion from the glandular hyperplasia is supplied by the placenta. He found that in the toxemic placenta cholinesterase activity is greatly increased. This observation was confirmed by Woodbury (24). This would cause an increased destruction of acetylcholine and upset the delicate balance of the system. With an already deficient liver function it would not take much decrease of acetylcholine to do this. He regards this dislocation of equilibrium, resulting from impaired destruction of vasopressor by the liver and acetyl-

choline deficiency in the placenta and blood, as the keystone to the interpretation of the diverse manifestations of late toxemia. He assigns the placenta merely the role of a determining factor in initiating and sustaining the increased activity of the pituitary, thyroid and adrenal glands. He believes that placental infarcts are the result of prolonged vasospasm in the placenta which is a part of the general vasopressor effect and are not of significance in producing symptoms by split-protein products from the necrotic tissue.

In applying this theory of etiology of toxemia to premature separation in particular, he believes the picture is due to increased histamine. This is due to the decreased histaminase previously mentioned, plus the autolysing syncytial fragments in the blood stream. The decreased histaminase is probably due to the general endocrine upset.

SUMMARY

The various possible causes of premature separation of the normally implanted placenta have been discussed. It has been shown that important factors are; trauma, vascular degenerative lesions of the placenta, infarcts, autolysing hematomas, and endocrine imbalance. There is a certain amount of evidence in favor of each one of these. A summary of the known facts are as follows:

a. Trauma can cause placental separation but it is

absent in the history of most cases.

b. Pathologic sections show degenerative vascular lesions in many cases.

c. There is a hypercholesterolemia in pregnancy.

d. Hemorrhagic infarcts are found in many cases.

e. Cases of concealed hemorrhage are more likely to have toxic symptoms than cases with external bleeding.

f. The picture of toxic premature separation can be produced experimentally with histamine.

g. The blood level of histaminase is decreased markedly in premature separation.

h. The blood level of histamine is increased in premature separation.

i. Histidine disappears from the urine of toxemic patients.

j. Antihistaminic drug appeared to cause improvement of the toxemia.

k. There is a similarity between some cases of premature separation with concealed hemorrhage and the "crush syndrome".

l. There is an antagonistic action between acetylcholine and the vasopressor substance.

m. There is increased cholinesterase in toxic placentae.

The mass of this evidence points toward histamine or some similar substance in the process of premature separation in many cases. The mode of formation of the substance is still much debated. In any case it comes from split-protein products of autolysing tissue whether as infarcts, hematomas, or syncytial buds. If it is to be considered a cause of the separation by virtue of its ability to cause increased permeability of vessel walls it must be present before the hematoma. If, as Bartholomew thinks, there is a spasmogenic influence on venous sphincters to cause an infarct which then autolyses, there must be some explanation of what causes the spasm. The only reason he gives is some possible pituitary or renal factor. Hofbauer's theory of syncytial buds and acetylcholine decrease explains more of the whole picture than any other theory thus far advanced. In some cases the picture seems to be complicated by absorption of substances from the autolysing hematoma causing a lower nephron nephrosis (crush syndrome) but this is not the basic cause of the separation.

If histamine is the cause of the toxic symptoms and the separation, antihistamine drugs should offer some hope in treatment. Hoffman's observations, if correct, seem to show this assumption to be true.

CONCLUSION

The basic etiology of premature separation of the

normally implanted placenta is not known. More evidence points to histamine or like substances than to other factors. The cause for the increased histamine has not been settled. There is probably some basic endocrine imbalance.

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