PRIMAL HEALTH RESEARCH

A NEW ERA IN HEALTH RESEARCH

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PRE-ECLAMPSIA, ECLAMPSIA
The Primal Health Research perspective

In order to illustrate the potential of the data bank, let us type some of the 300 or so terms included in the key-words index. Some of these key-words offer a retrospective orientation: if we type "asthma", for example, we shall be oriented towards events that happened during the primal period. The other key-words offer a prospective orientation. We'll take "pre-eclampsia" as an example. A glimpse at the list of the eight studies that match at the key word "pre-eclampsia" immediately indicates that we are breaking through the usual frontiers of medical specialization.

Let us recall that pre-eclampsia is a disease of late pregnancy (usually first pregnancy). It is life threatening for baby and mother. Early detection of this disease has been originally the main reason for introducing the concept of pre-natal care during the twentieth century. According to the most common definitions, pre-eclampsia implies the association of high blood pressure (more than 140/90 after rest on at least 2 occasions) and presence of more than 300 mg of protein in the urine per 24 hours (presence that is not related to urinary tract infection). There are usually other detectable metabolic imbalances, such as high blood levels of uric acid, low platelet counts and other aspects of the HELLP syndrome. When there are seizures the disease is called eclampsia (the entries opened via the key-word "eclampsia" are also opened via "pre-eclampsia").The old term toxaemia - that included pre-eclampsia and eclampsia - is now out of fashion.

Pre-eclampsia is overdiagnosed, because it is often confused with pregnancy-induced hypertension, which is not a disease when it is not associated with metabolic disturbances. We previously mentioned that the tendency to overdiagnose pre-eclampsia is one of the most common causes of the "nocebo effects" of antenatal care (see Vol 7 No 4: antenatal scare).

Three Swedish studies relate a pre-eclamptic or eclamptic state of the mother when she was about to give birth and the risk for her daughter to have one day a breast cancer(1,2,3). The

last of these studies, published in 1997, confirms and enlarges the previous ones. The authors had at their disposal the birth records of all deliveries at five different hospitals between 1874 and 1961. 1068 women with a breast cancer were traced. The 2727 control subjects were matched for date of birth. There was a markedly reduced risk for breast cancer in women whose mothers had pre-eclampsia or eclampsia, and an excess risk in women who had neonatal jaundice. Because pre-eclampsia is associated with low levels of oestrogens, and neonatal jaundice with high levels, the authors conclude that oestrogens may play a critical role during the intrauterine period in regard to the risk of breast cancer in adulthood. Such a link between pre-eclampsia and breast cancer incites to type the key word "breast cancer" and to go backwards. It will appear that the risks for a woman of having a breast cancer in adulthood are to a great extent determined during fetal life.

These studies have some similarities with a study by the same team about prostate cancer(4). The authors had at their disposal the birth records of men born at Uppsala University Hospital between 1874 and 1946. They established a study group of 250 men with prostate cancer (or who died from prostate cancer), and a matched control group of 691 men (including 196 dead). The most striking difference between the two groups is that none of those having prostate cancer had a pre-eclamptic mother, versus 13 among the controls. In other words pre-eclampsia or eclampsia predicted a very low risk of prostate cancer.

Pre-eclampsia represents a risk for the child to be admitted to hospital later on in life with a diagnosis of schizophrenia. This is one of the main conclusions of a study covering all psychiatric hospital admissions and all hospital deliveries in Scotland since 1971 (5). It was possible to compare the obstetric records of 115 schizophrenics and of the same number of controls. There was a significant excess of pre-eclampsia in the study group (10 versus 2). The link between pre-eclampsia and schizophrenia offers another example of the possibility to use the data bank with forwards and backwards motions. Today a great number of studies suggest that the chain of events leading to schizophrenia begins during fetal life.

A study from Baltimore about mental retardation has a historical interest because it was published as early as 1955(6). The authors studied the background of 1107 children born between 1935 to 1952, whose IQ was under 80. Data about the perinatal period were obtained from the birth register of Baltimore City Health Department. The main conclusion was that non-mechanical complications such as "toxaemia" (and also bleeding in pregnancy) appear to be more important than the mechanical factors. A year later the same team published a study of all persons born in Baltimore after 1939 and referred to the division of special services of the Baltimore Department of Education for "behaviour disorder"(7). 1151 cases and 902 controls were found and studied. Pre-eclampsia appeared to be a significant risk factor.

A study of cerebral palsy is of special interest at a time when the focus is more on the prenatal risk factors than on the perinatal risk factors. This study involved 59 very preterm babies who developed cerebral palsy and were compared 334 controls(8). One of the most interesting findings is that pre-eclampsia is associated with a reduced risk of cerebral palsy. Let us notice that in this study none of the mothers had been treated by magnesium sulphate (the magnesium sulphate by itself may reduce the risk of cerebral palsy). The results of this study fit perfectly with our understanding of the nature of pre-eclampsia and eclampsia.

PRE-ECLAMPSIA AS A MOTHER-BABY CONFLICT

Looking at dogs to understand humans

Interspecies comparisons

Veterinarians use the word eclampsia to refer to a life-threatening disease that can occur in different mammals such as dogs. The typical story is that of a bitch whose litters are large. At the end of her pregnancy or at the beginning of lactation the bitch will be restless and nervous. Within a short time she will walk with a stiff gait and may even wobble or appear disoriented. Eventually she may be unable to walk and exhibit extreme leg rigidity. Death can occur if no treatment is given. For the veterinarians there is no doubt that this disease is the consequence of a conflict between mother and babies. The bodies of some bitches simply cannot keep up with the increased demands in nutrients, particularly calcium. In other words there is a conflict between the demands expressed by the fetuses and what the mother can do without depleting her own body. This interpretation is confirmed by the spectacular effect of an intravenous calcium supplementation. One must emphasise that where dogs are concerned the priority at the end of pregnancy and the beginning of lactation is to feed the bones of the babies, that are much more mature at birth than those of humans. It is therefore not surprising that in this species the so-called eclampsia is in fact mostly related to low calcium levels (it is a "puerperal tetany").

The concept of a possible conflict between mother and fetus is supported by genetic considerations. David Haig, from the museum of comparative zoology at Harvard University, expressed the fruitful theory of genetic conflict in pregnancy (9,10). He judiciously stressed that mother and fetus do not carry identical sets of genes: in the child there are maternally derived genes and also paternally sets of genes. Put in other words the harmony of interests between mother an fetus cannot be complete.

What about the big-brained ape?

If there is a possible conflict in mammals between genes expressed in the mother and genes expressed in the fetus/placenta, this leads to inevitable questions regarding the possible reasons for a mother-offspring conflict in the human species. Among humans the priority is not to have strong bones at birth. The priority is to feed the developing brain. The spectacular brain growth spurt during the second half of fetal life is a specifically human trait. Let us recall that the size at birth of the human brain is a quarter of the adult size, whereas the size of the whole body is only a twentieth of the adult size. One can conclude that in our species, when there is a conflict between the demands expressed by the fetus and what the mother can do without depleting her body, we should look first at the huge needs of the developing brain.

Today the specific needs of the developing brain are well understood. Sixty per cent of the brain is made of fat. This means that the main nutritional needs are in terms of fatty acids. The developing brain has special needs in long chain polyunsaturated fatty acids from the omega 6 and omega 3 families. More precisely at least fifty per cent of the molecules of fatty acids which incorporate into the brain are represented by one molecule usually called DHA (an abbreviation for docosahexaenoic acid). This long chain polyunsaturate belongs to the omega 3 family (22 C and 6 double bonds). One can therefore assume that the most likely reason for a conflict in pregnancy among humans is when the mother cannot keep up with the increased demands in DHA. An imbalance in the mother's body - a disease - will be the price to pay so

that the needs of the developing brain can be met. (Let us mention right away that the long chain fatty acids of the omega 3 family are abundant and preformed in the sea food chain). An interspecies study of the effects of maternal-fetal conflicts incites to establish a hierarchy between the numerous well documented biological imbalances associated with pre-eclampsia among humans. The first step should be to look at the maternal fatty acids status at the end of normal pregnancy and in pre-eclampsia. We should look particularly at the group of long chain omega 3 polyunsaturates, that includes DHA and also a parent molecule with 20 carbones and 5 double bonds commonly called EPA (an abbreviation for eicosapentaenoic acid). These two members of the same group are interconvertible in the human body. EPA does not incorporate into the brain, but its metabolites represent the series 3 of prostaglandins. It is well known that there are significant increases of both EPA and DHA in normal pregnancy.

In our view the central imbalance in human pre-eclampsia is the enormous discrepancy between the maternal plasma levels of DHA and EPA. In pre-eclampsia the level of DHA is not significantly decreased while the level of the parent molecule EPA is about 10 times lower than in normal pregnancy (11). This is exactly the data we are expecting when assuming that brain development is a priority among humans. Such data is confirmed (12) by a study evaluating the comparative ratio of DHA to EPA in maternal platelets of normotensive and pre-eclamptic women (7.82 versus 11.00). Whatever the circumstances the levels of one of the most important molecules for brain development remain stable. The price is an imbalance inside the family of omega 3 fatty acids that is at the root of a long chain of imbalances.

This is how one can understand the onset of a vicious circle when the fetal brain develops dramatically and the demand in long chain fatty acids is maximum: at that stage, if the amount of omega-3 polyunsaturates available is low, the priority is to maintain the level of DHA as stable as possible. Yet it has been demonstrated that a diet poor in omega-3 fatty acids is a risk factor for pre-eclampsia. By analysing the fatty acids contents of the red blood cells of pregnant women it is possible to evaluate the sort of lipids they have consumed during the previous three months. A study using this method (13) demonstrated that women with the lowest levels of omega-3 fatty acids were 7.6 times more likely to have had their pregnancies complicated by pre-eclampsia as compared with those women with the highest levels of omega 3. A 15% increase in the ratio of omega-3 to omega-6 was associated with a 46% reduction in risk of pre-eclampsia. When the amount of omega-3 available is low, the first compensatory effect - in order to maintain a sufficient amount of DHA available - is the collapse of the level of the parent molecule EPA: this is probably the main precipitating factor. It explains the well known imbalances in the system of prostaglandins and particularly the decreased ratio of prostacyclin to thromboxane-2. When the level of EPA has collapsed there is no production of the physiologically inactive thromboxane-3. This leads to an overproduction of the physiologically active thromboxane-2, through a mechanism of enzymatic competition. Moreover, when the level of EPA is low, there is no production of the physiologically active prostacyclin-3. In normal pregnancy the ratio of prostacyclin to thromboxane-2 in maternal blood progressively favours prostacyclin. Let us recall that prostacyclin is a potent vasodilator, an inhibitor of platelet aggregation and an inhibitor of uterine contractility. Thromboxane has opposite actions.

Puzzling aspects of pre-eclampsia

Any theoretical vision of pre-eclampsia must be confronted with the most intriguing aspects of the disease.

Pre-eclampsia is principally a disease of first pregnancies. Yet it has been demonstrated that the metabolism of omega-3 fatty acids is influenced by parity (14,15). It is as if brain development is a more absolute and unconditional priority in the case of a first baby: the DHA content of cord blood phospholipids depends on birth order; in other words, the capacity to provide preformed DHA is depleted with repeted pregnancy.

We mentioned a study in our data bank suggesting that pre-eclampsia is associated with a reduced risk of cerebral palsy. In our view the occurrence of pre-eclampsia implies that fetal brain development has been such an unconditional priority that there has been a transfer of nutrients (in particular DHA) in excess of the maternal safety limit. The consequence of preserving the needs of the developing brain at any price may be a life threatening disease...but the risk of cerebral palsy is reduced.

It is easy to propose an interpretation of the increased risk of pre-eclampsia in twin pregnancies: two brains must be fed. The possible association between hydatiform mole and pre-eclampsia supports the theory of genetic conflict in pregnancy. In the case of an hydatiform mole, there is an excessive placental proliferation without associated fetal tissues; significantly there are two paternal genomes but no maternal genomes. It suggests that it is probably via HCG that the placenta manipulates maternal physiology in order to maintain high levels of DHA available.

Even the high level of DHA in pre-eclampsia has been considered as enigmatic. The authors of a Dutch study were intrigued at such a point that they raised the possibility that fish oil supplementation may be contraindicated in pregnancy (16). There is no enigma if the focus is on the collapse of the parent molecule EPA, and if the link between pre-eclampsia and brain development is understood.

Practical implications. How to prevent pre-eclampsia

Not only can we propose a hierarchy between well documented biological imbalances, but we can also establish links between different approaches that have been tested to prevent pre-eclampsia.

It seems difficult to effectively act at the very beginning of the chain of event, that is at the time of placental implantation. Today it is well accepted that there is originally a faulty placentation in women destined to have pre-eclampsia (17). The fact that a previous miscarriage (18), a previous blood transfusion (19), or a long sexual cohabitation before conception (20) reduce the risk of pre-eclampsia confirm the probable importance of the immune response at that phase. On the other hand it seems easier to try to neutralize the precipitating factors in the second half of pregnancy.

The most direct way to prevent pre-eclampsia is theoretically to consume sea fish. Let us stress that the fish that are rich in omega 3 are not polluted, because they swim in the high sea and are at the beginning of the sea food chain (sardines, pilchards, herrings, mackerel, salmon, etc.). This is in agreement with the geographical variations in the rates of pre-eclampsia.

During the years 1991 and 1992, in a London hospital, I interviewed at random 499 pregnant women before 20 weeks gestation, in addition to their routine prenatal care. They were encouraged to increase their intake of oily sea fish. A hospital and parity matched control of 500 women was established(21). There were no eclampsia or pre-eclampsia in the study group, versus one eclampsia and two pre-eclampsia in the control group. We need large studies of this kind in order to reach significant conclusions. Let us mention a Danish study of fish oil supplementation. It was only indicated in the full text that there was no pre-eclampsia in the study group versus five in the control group. Those who read the abstract only just remembered that fish oil supplementation, provided in the third trimester of normal pregnancy, showed no effect on blood pressure(16). One must keep in mind that eating fish is not the same as taking supplements of fish oils.

For those who cannot consume sea food a great importance must be given to catalysts of the metabolism of unsaturated fatty acids, insofar as only the precursor in the omega 3 family (with 18 carbons and 3 double bonds) is abundantly provided by the plants of the land food chain. Magnesium is one of these catalysts, and the preventive and even curative effects of magnesium sulphate are well known(22). Calcium is another catalyst and many studies have evaluated its preventive effects(23); a century ago A Pinard, in Paris, had already demonstrated that a milk diet could reduce the risk of eclampsia (24); one must underline that milk is also a source of high quality proteins and also of arachinodic acid, an omega 6 polyunsaturate essential for brain development; moreover there is a low incidence of pre-eclampsia among Mayan Indians (25) and Ethiopians (26), whose diets are exceptionally rich in calcium. Zinc is also a well-known catalyst of delta-6 desaturation and low zinc concentrations have been reported in pre-eclampsia (27). It is worth mentioning that fish represent a good source for such minerals.

It also makes sense, in order to prevent pre-eclampsia, to reduce as much as possible the level of blocking agents of the metabolic pathways of unsaturated fatty acids. Among them are the trans fatty acids (abundant in processed oils, conventional margarines, cookies, French fries, fast food, etc.). It is significant that the risk of preclampsia is correlated with the level of trans-fatty acids in maternal red blood cells, and therefore with dietary intake (28). Alcohol, pure sugar are also blocking agents and should be theoretically avoided. Hormones such as cortisol are also known blocking agents. This can explain how the emotional state of the pregnant woman is a factor influencing the risk of pre-eclampsia(29).

It is also theoretically important to avoid a fast destruction (via peroxidation reactions) of the long chain fatty acids available. Yet lipids peroxides are increased in pre-eclampsia. That is why, during pregnancy, there is an enhanced need in antioxidants such as vitamin E, vitamin C, carotenoids, flavonoids, selenium, etc.) . The preventive effects of antioxidants is well documented(30). It is significant that in the regions where the soil is deprived in selenium (e.g. the Heilongjiang province in China) the rates of pre-eclampsia are exceptionally high (31). Let us underline that sea fish are also rich in selenium.

Food from the land and food from the sea

It is theoretically easier to meet the enormous needs of the developing human brain when the diet includes some food from the sea. Our focus has been on the molecules of fatty acids which are preformed and abundant in the sea food chain. The sea food chain has other characteristics. For example any sea food is rich in iodine, which is essential for brain development, insofar as it is a major component of thyroid hormones. Among the numerous

documented imbalances in pre-eclampsia, those regarding thyroid hormones should not be overlooked.

Finally it appears that pregnant women (and probably Homo Sapiens in general) ideally need a certain balance between food from the land and food from the sea. One can propose that pre-eclampsia is the price some human beings must pay for having a large brain while they are more or less separated from the sea food chain.

REFERENCES

1. Ekbom A, Trichopoulos D, et al. Evidence of prenatal influence on breast cancer risk. Lancet 1992; 340: 1015-18.
2. Ekbom A, Thurfjell E. et al. Perinatal characteristics and adult mammographic patterns. Int J of Cancer 1995; 61: 177-80.
3. Ekbom A, Hsieh CC, et al. Intrauterine environment and breast cancer risk in women: a population-based study. J Natl Cancer Inst 1997; 89: 71-76.
4. Ekbom A, Hsieh CC, et al. Perinatal characteristics in relation of and mortality from prostate cancer. BMJ 1996; 313: 337-41.
5. Kendell RE, Juszczak E, Cole SK. Obstetric complications and schizophrenia: A case control study based on standardised obstetric records. Br J Psychiatry 1996; 168: 556-61.
6. Pasamanick B, Lilienfeld AM. Association of maternal and fetal factors with development of mental deficiency. JAMA 1995; 159(3): 155-60.
7. Pasamanick B, Rogers ME, Lilienfeld AM. Pregnancy experience and the development of behavior disorder in children. Am J of Psychiatry 1956; 112: 613-18.
8. Murphy DJ, Sellers S, et al. Case-control study of antenatal and intrapartum risk factors for cerebral palsy in very preterm singleton babies. Lancet 1995; 346: 1449-54.
9. Haig D. Genetic conflicts in human pregnancy. The Quarterly Review of Biology 1993; 68 (4); 495-531.
10. Haig D. Altercation of generations: genetics conflicts of pregnancy. Am J Reprod Immunol 1996; 35 (3): 226-36.
11. Wang Y, Kay HH, Killam AP. Decreased levels of polyunsaturated fatty acids in pre-eclampsia. Am J Obstet Gynecol 1991; 164: 812-18.
12. Velzing-Aarts FV, Van der Klis FRM, et al. Umbilical vessels of preeclamptic women have low contents of both n-3 and n-6 long-chain polyunsaturated fatty acids. Am J Clin Nutr 1999; 69: 293-98.
13. Williams MA, Zingheim RW, King IB, Zebelman AM. Omega-3 fatty acids in maternal erythrocytes and risk of pre-eclampsia. Epidemiology 1995; 6: 232-37.
14. Carlson E, Salem N. Essentiality of omega-3 fatty acids in growth and development in infants. In: Simopoulos AP, et al (eds): "Effects of polyunsaturated fatty acids in seafoods". World Rev Nutr Diet; Basel, Karger 1991; 66: 74-86.
15. Al MDM, Van Houwelingen AC, Hornstra G. Relation between birth order and the maternal and neonatal docosahexaenoic acid status. Eur J Clin Nutr 1997; 51: 548-53.
16. Al MDM, Van Houwelingen AC, et al. The essential fatty acid status of mother and child in pregnancy-induced hypertension: a prospective longitudinal study. Am J Obstet Gynecol 1995; 172: 1605-14.
17. De Groot CJM, O'Brien TJ, Taylor RN. Biochemical evidence of impaired trophoblastic invasion of decidual stroma in women destined to have pre-eclampsia. Am J Obstet Gynecol 1996; 175: 24-29.
18. Strickland DM, Gusik DS, et al. The relationship between abortion in the first trimester and development of pregnancy-induced hypertension in subsequent pregnancy. Am J Obstet Gynecol 1986; 154: 146-48.
19. Feeney JC, Tovey LAD, Scott JS. Influence of previous blood transfusion on incidence of pre-eclampsia. Lancet 1977; ii: 874-75.
20. Robillard PY, Husley TC, Perianiu J, et al. Association of pregnancy-induced hypertension with duration of sexual cohabitation before conception. Lancet 1994; 344: 973-75.
21. Odent M, McMillan L, Kimmel T. Prenatal care and sea fish. Eur J Obstet Gynecol 1996; 68 (1,2): 49-51.
22. Eclampsia Trial Collaborative Group. Which anticonvulsivant for women in pre-eclampsia? Lancet 1995; 345:1455-63.
23. Bucher HC, Guyatt CH, Cook RJ, et al. Effect of calcium supplementation on pregnancy-induced hypertension and pre-eclampsia. JAMA 1996; 275: 1113-17.
24. Pinard A. Esquisse des progres realises en obstetrique pendant le 19em siecle. Annales de gynecologie et d'obstetrique, decembre 1900: 11-13.
25. Belizan JM, Billar J. The relationship between calcium intake and edema, proteinuria and hypertension-gestosis: an hypothesis. Am J Clin Nutr 1980; 33: 2202-10
26. Hamlin RHJ. The prevention of eclampsia and pre-eclampsia. Lancet 1952; 1: 64-68.
27. Kiilhoma P, Pakarinen P, Gronroos M. Copper and zinc in pre-eclampsia. Acta Obstet Gynecol Scand 1984; 63: 629-31.
28. Williams MA. Risk of pre-eclampsia in relation to elaidic acid (transfatty acid) in maternal erythrocytes. SPO abstracts. In: Am J Obstet Gynecol 1995; 436: 380.
29. Kurki T, Hiilesmaa V, Raitasalo R, et al. Depression and anxiety linked to pre-eclampsia. Obstet Gynecol 2000; 95: 487-90.
30. Chappell LC, Seed PT, et al. Effects of antioxidants on the occurrence of pre-eclampsia in women at increased risk: a randomised trial. Lancet 1999; 354: 810-16.
31. Lu B, Zhang SW, Huang B, et al. Changes in selenium in patients with pregnancy-induced hypertension. Chinese J Obstet Gynecol 1990; 25: 325-27.
32. Odent M. Primal Health. Century-Hutchinson. London 1986 (out of print)
33. Seymour-Reichlin. Neuroendocrine – immune interaction. N Engl J Med1993; 329:1246-53.

GLOSSARY

We propose a vocabulary adapted to the new scientific context.

Primal - first in time and first in importance.

Primal period - the time which included fetal life, perinatal period and early infancy. It is during the primal period that the adaptive systems involved in what we commonly call health reach maturity. It is the time of close dependence on the mother. One can anticipate that any kind of event happening during this period can have irreversible effects.[32]

Primal adaptive system - the subcortical nervous system, the endocrine system and the immune system should no longer be separated and should be understood as a whole (e.g. the brain is a gland, insulin is a neuromediator, lymphocytes can release endorphins, etc.). We call this network the 'primal adaptive system'. Phrases used in the medical literature, such as 'psychoneuroimmuno endocrinological system', 'psychoneuro immunology', immuno endocrinology', etc., should be expressed in simpler terms. A recent review-article in the *New England Journal of Medicine* gave a perfect updated description of what we call the 'primal adaptive system'.[33]

Health - is how well the primal adaptive system works (it is not the absence of disease).

At the end the primal period we are in a basic state of health called **primal health.** The objective of **primal health research** is to explore correlations between the Primal period and what will happen later on.

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