

PRIMAL HEALTH RESEARCH

A NEW ERA IN HEALTH RESEARCH

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PROJECTS

We are now starting a new series of our newsletter. This series of fifty issues should continue to summer 2018. The previous issue (volume 13, no. 2) was the last one of a series of fifty that started in summer 1993. Now we need a special edition to take a deep breath, to pause for thought, to look toward the future, and to choose our priorities for the next twelve years. In other words, this special edition concerns important projects.

After presenting two of our imminent projects, we'll continue our series of essays inspired by lessons we can learn from the Primal Health Research Data Bank. Volume 13, no. 4 will explore 'antisocial behaviours from a Primal Health Research perspective'... an obligatory subject for those who want to deepen their understanding of Homo Sapiens as a gregarious primate.

PROJECT 1:
WOMBECOLOGY.COM

Our first project is a website called 'wombecology.com'. The objective is to communicate with all those who have not yet recognized prenatal ecology as the most vital branch of ecology, and to present the fetal phase of human life as the period of greatest vulnerability and adaptability to environmental factors. This site will be intended primarily for 'ecologists', who are familiar with such concepts as *ecological sciences, ecological technology, ecological philosophy, ecological politics, ecological awareness, ecojobs, or ecotourism*, but who have not yet realised that all efforts to "save the planet" cannot succeed until the advent of an *ecological human being*.¹

Although www.wombecology.com will be completed by March 2006, it is already possible to preview its contents by visiting the front page. Fetal life will be divided into *pre-labour intrauterine life* and *in-labour intrauterine life*. Apart from the usual practical pages (*sources, links, contact us, etc.*) we'll pay special importance to the needed mutation from *Homo Super-predator* to *Homo Ecologicus*. Two basic and related questions are: "How to develop respect for Mother Earth?" and "How to develop a compassionate concern for future unborn generations?" In this age of *The Scientification of Love*² we can suggest answers to such questions.

Thomas Verny coined the term *womb ecology*, during his 1991 presidential address at the 5th International Congress of the Pre- and Perinatal Psychology Association of North America (PPPANA) in Atlanta, Georgia. He provided the keys for the advent of an ecological human being through a remarkably concise equation:
Womb ecology = World ecology² Thank you, Thomas!

PROJECT 2: **NUTRITION AND ECLAMPSIA**

We recalled in previous issues that more than half a million of deaths related to pregnancy and birth occur every year in the world, according to the most authoritative public health reports.³ Eclampsia is a main component of maternal mortality, accounting for about 50,000 deaths worldwide.⁴ The prevalence of eclampsia varies widely according to standards of living. A study of the efficacy of treatment with magnesium sulphate, conducted at Dhaka Medical College and Hospital, Bangladesh, included 2956 consecutive eclamptic women admitted between 1998 and 2000.⁵ Meanwhile, researchers in Wolverhampton, England, replicated and enlarged our previous study at an East London Hospital of nutrition in pregnancy.⁶ In a series of more than 3000 births they could not detect a single case of eclampsia and the risks of pre-eclampsia were so low that it was impossible to draw any significant conclusions (data not yet published). The enormous disparity in the prevalence of eclampsia according to living standards suggests nutritional factors are influential.

Yet most researchers focus on wealthy populations. In such a context they investigate mild forms of the disease and ignore nutritional factors. Their usual main objective is to develop tests for the early prediction of pre-eclampsia. Such studies cannot help improve our understanding of the genesis of the disease nor can they reduce the rates of maternal deaths in poor countries. To achieve significant conclusions, large studies are needed among populations where the rates of genuine eclampsia are still high. Eclampsia is an easy diagnosis, since it is associated with convulsions and the mother eventually passes into a coma. Thus, such studies are feasible among poor populations and provide the reason for our second project.

This project was born on December 6, 2005, when I visited the Alexander Fleming hospital in a poor district of Rio de Janeiro. There I met Antonio Carlos Cavaliori, the head of a huge department of obstetrics (6000 babies born per year) where

eclampsia is still common. I also met Silma Nagipe, who described her PhD projects. This is how we conceived of a randomised controlled trial to give canned sardines to a certain number of pregnant women as early as possible. The first objective would be to evaluate the effects of this intervention on the incidence of eclampsia.

Of course, we now have to consider many practical issues, especially the feasibility of such a study in that particular hospital where the members of the staff are untrained in research. We also have to explore possible sources of funding. I offer a reprint of my paper in *MedGenMed* dated September 5, 2001 to aid in understanding the hypothesis we want to test. Sections of the text that are directly related to our project are underlined.

Michel Odent

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REPRINT

NOTE: To view the article with Web enhancements, go to:
<http://www.medscape.com/Medscape/GeneralMedicine/journal/2001/v03.n05/mgm0905.01.odent/mgm0905.01.odent-01.html> <[mgm0905.01.odent-01.html](http://www.medscape.com/Medscape/GeneralMedicine/journal/2001/v03.n05/mgm0905.01.odent/mgm0905.01.odent-01.html)>.

Hypothesis: Preeclampsia as a Maternal-Fetal Conflict

[MedGenMed September 5, 2001. © 2001 Medscape, Inc.]

Michel Odent, MD

Abstract

The association of preeclampsia with both high and low birth weight challenges the current belief that reduced uteroplacental perfusion is the unique pathophysiologic process in preeclampsia. Preeclampsia is thus presented from a new perspective, in the framework of maternal/fetal conflict.

Interspecies comparisons encourage us to raise new questions concerning the potential for conflict among humans. The spectacular brain growth spurt during the second half of fetal life is a specifically human trait. A conflict between the demands expressed by the fetus and what the mother can do without depleting her body leads us to consider first the needs of the developing brain.

Introduction

There is a widespread belief that reduced uteroplacental perfusion is the central pathophysiologic process in preeclampsia. This belief is challenged by several puzzling aspects of the disease. For example, a study[1] looking at 97,270 births in 35 hospitals in Alberta, Canada, revealed that there is a significant association between preeclampsia and large-for-gestational-age infants, in addition to the well-known association with small-for-gestational age infants. Such findings are more easily interpreted if this multifactorial syndrome is presented as an expression of a maternal/fetal conflict. From this perspective, it is plausible that a large fetus's high demand for nutrients can be the root of conflict. Faulty placentation, inadequate maternal nutrition, and certain combinations of maternal and fetal genotypes are other factors that can independently increase the probability of conflict.

The common tendency to confuse gestational hypertension -- which is not associated with proteinuria -- and preeclampsia is an obstacle to understanding the nature of the disease. Several epidemiologic studies confirm that gestational hypertension is followed by good perinatal outcomes.[2-5] According to the most common definitions, preeclampsia implies the association of high blood pressure and the presence of more than 300 mg of protein in the urine per 24 hours (unrelated to urinary tract infection). There are usually other detectable metabolic imbalances.

A Fruitful Theory

The concept of maternal fetal conflict is supported by the theory of genetic conflict in pregnancy proposed by David Haig.[6,7] Haig stresses that, among mammals in general, mother and fetus do not carry identical gene sets. In other words, maternal and fetal interests are not always in harmony. Maternal genes, maternally derived genes in the current child, and paternally derived genes in the current child lay the foundation for a

conflict of interest. The maternal-fetal relationship has been shaped by a history of evolutionary conflict. Many characteristics of human pregnancies may be interpreted in the framework of genetic conflict (eg, nausea and vomiting, variations in the duration of pregnancy, eclampsia).

Haig's theory, together with data from veterinary medicine, helps us to understand that the nature and the expression of such conflicts differ according to the species of mammals being considered.

For example, veterinarians use the term eclampsia to refer to a life-threatening disease that occurs in various mammals, including dogs. In this species, the so-called eclampsia is in fact related to hypocalcemia (it is a "puerperal tetany"). Of course, where dogs are concerned, the priority at the end of pregnancy and at the beginning of lactation is development of the bones of the offspring, which are much more developed at birth than the bones of other mammalian species.

Interspecies comparisons encourage us to raise new questions concerning the potential for conflict among humans. The spectacular brain growth spurt during the second half of fetal life is a specifically human trait. A conflict between the demands expressed by the fetus and which of those demands the mother can fulfill without depleting her body leads us to consider first the needs of the developing brain.

Specific Needs of the Developing Brain

Sixty percent of the brain is made of fat. This means that the main nutritional needs are in terms of fatty acids.[8] The developing brain has special needs for long-chain polyunsaturates from the n-6 and n-3 families, particularly arachidonic acid (AA = 20:4 n-6) and docosahexaenoic acid (DHA = 22:6 n-3). More precisely, at least 50% of the molecules of fatty acids that incorporate into the brain are represented by DHA. One can therefore assume that the most likely reason for a conflict is when the mother cannot keep up with the increased demands for DHA. A disease will be the price the mother's body has to pay to meet the needs of the developing brain.

The concept of maternal-fetal conflicts directs us to establish a new classification of the numerous well-documented biological imbalances associated with preeclampsia among humans. The first step should be to look at the status of maternal fatty acids at the end of normal pregnancy and in preeclampsia. We should look particularly at the group of long-chain n-3 polyunsaturates, which includes DHA and eicosapentaenoic acid (EPA = 20:5 n-3). 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.

It seems that the central imbalance in human preeclampsia is the enormous discrepancy between the maternal plasma levels of DHA and EPA.[9] In preeclampsia, the level of DHA is not significantly decreased, whereas the level of the parent molecule EPA is about 10 times lower than in normal pregnancy.[10] These are exactly the data we are expecting when assuming that brain development is a priority among humans. Such data are confirmed by the "Curacao study,"[11] which compared the fatty acid compositions of maternal and umbilical cord platelets from preeclamptic and normotensive (control) women. The comparative ratio of DHA to EPA in maternal platelets of normotensive and preeclamptic women was 7.82 vs 11.00. The level of DHA was not significantly higher in the platelets of preeclamptic women (2.16 vs 2.03), whereas the level of EPA was

significantly lower (0.21 vs 0.29; $P < .05$). Whatever the circumstances, the levels of DHA remain stable. This fact is noticeable when keeping in mind the paradoxically low delta 4 -desaturase activity among humans (DHA is a delta 4 -desaturase product).[12] The price of a stable DHA is an imbalance inside the family of n-3 fatty acids that is at the root of a long chain of further imbalances.

This is how one can understand the onset of a vicious circle when the demand in long-chain fatty acids is at its greatest: at that stage, if the amount of n-3 polyunsaturates available is low, the priority is to keep the level of DHA as stable as possible.

The use of biochemical markers of dietary intakes of lipids has demonstrated that a diet poor in n-3 fatty acids is a risk factor for preeclampsia. Studies of the erythrocyte fatty acids profile reflect the dietary fat intake over a 2- to 3-week period. One such study[13] found that women with the lowest levels of n-3 fatty acids were 7.6 times more likely to have had their pregnancies complicated by preeclampsia as compared with those women with the highest levels of n-3. A 15% increase in the ratio of n-3 to n-6 was associated with a 46% reduction in the risk of preeclampsia. Evaluating the fatty acid compositions of maternal platelets is another way to use biological markers of dietary fat intake.

According to the Curacao study,[11] the ratio of AA to EPA is significantly higher in maternal platelets of preeclamptic women (109.13 vs 78.13; $P < .05$).

These concordant and significant data suggest that when the amount of n-3 available is low, the first compensatory effect -- in order to maintain an adequate supply of DHA available -- is the collapse of the level of the parent molecule EPA: this precipitating factor 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 favors prostacyclin.

Puzzling Aspects of Preeclampsia

Any theory of preeclampsia must address the following intriguing aspects of the disease.

- Preeclampsia is principally a disease of first pregnancies. We must recall that the metabolism of n-3 fatty acids is influenced by parity.[14,15] The DHA content of cord blood phospholipids depends on birth order; in other words, the capacity to provide preformed DHA is depleted with repeated pregnancies. It is as if brain development is a higher priority in the case of a first baby.
- The reported association of preeclampsia with a reduced risk of cerebral palsy is also intriguing.[16] The consequence of preserving the needs of the developing brain at any price may be a maternal 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. It is of interest that a case of intrauterine death of a twin was followed by the resolution of the symptoms and signs of preeclampsia: the pregnancy continued safely for a further 7 weeks.[17]
- The possible association between hydatiform mole and preeclampsia 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; there are 2

paternal genomes but no maternal genomes. The association of hydatiform mole and high levels of human chorionic gonadotropin (HCG) suggests that, in the case of preeclampsia, it is mostly via HCG that the placenta manipulates maternal physiology for fetal benefit.

- The comparatively high level of DHA in preeclampsia has been considered enigmatic: the possibility that fish oil supplementation may be contraindicated in pregnancy has even been raised.[18] There is no enigma if the focus is on the collapse of the parent molecule EPA -- or if we understood the link between preeclampsia and brain development.

Practical Implications: Prevention of Preeclampsia

This perspective offers much more than a new classification of biological imbalances and future avenues for research. It can also establish links between different approaches that have been used in the effort to prevent preeclampsia.

Effective preventive action at the very beginning of the chain of events -- at the stage of faulty placental implantation -- cannot be considered.[19] The fact that a previous miscarriage,[20] a previous blood transfusion,[21] or a long sexual cohabitation before conception[22] reduces the risk of preeclampsia confirms the probable importance of the immune response during that phase. It seems more realistic, on the other hand, to try to moderate the effects of the precipitating factors during the second half of pregnancy.

Theoretically, the most direct way to prevent preeclampsia would be to consume sea fish that is rich in n-3 polyunsaturates and also in minerals that are essential nutrients for the brain (eg, iodine, selenium, and zinc). This conforms with the geographical variations in the rates of preeclampsia and with the results of our encouragement of pregnant women to eat fish from the sea.[23] In order to reach significant conclusions, large studies of this kind are needed in countries where the rates of preeclampsia and eclampsia are high. We must keep in mind that extremely high maternal mortality ratios of over 1000 per 100,000 live births are observed in Eastern and Western Africa, and eclampsia is one of the main causes of maternal death. Eclampsia is an easy diagnosis, which makes such intervention studies feasible in third-world countries. One can imagine providing supplements of canned sardines to a research population of pregnant women. The need for such studies is supported by the fact that, among the Swedish, significantly lower risks of preeclampsia were observed for women born outside Nordic countries -- that is, in countries with much higher rates of preeclampsia.[24] It is probable that immigration is associated with significant changes in diet.

Until now, all studies have been conducted in wealthy countries with very low rates of preeclampsia, such as Scandinavian countries. These studies usually involved controlled trials of fish oil supplementation which began during the second half of pregnancy (fish oil supplementation should not be confused with the consumption of sea fish). Based on the results of several studies, preeclampsia has not been dissociated from the framework of pregnancy-induced hypertension. For many reasons, it is therefore not surprising that meta-analyses[25] and systemic reviews[26,27] have found insufficient evidence of the effects of fish oil on the risk of preeclampsia. In fact, most studies were too small to even address the issue of preeclampsia.

For example, a Danish study involved 533 healthy women randomly assigned in a ratio of 2:1:1 to receive, after 30 weeks pregnancy, either fish oil, olive oil, or no oil supplementation.[28] The objective was to evaluate the effects of fish oil on the duration

of pregnancy. There was no mention of the rate of preeclampsia or eclampsia. The same study was published in another context, with the effect on blood pressure as a new objective.[29] Again, there was no mention of the rate of preeclampsia in the tables or in the abstract, and the abstract conclusions did not stimulate curiosity. For example: "2.7 g/day of marine omega-3 fatty acids, provided in the third trimester of normal pregnancy, showed no effect on blood pressure." In fact, it was mentioned only in the detailed text that no preeclampsia occurred in the fish oil group vs 5 cases in the control group.

We might make similar comments about our own study, conducted during the years 1991-1992 in a London hospital.[23] We randomly selected 499 pregnant women and encouraged them to increase their intake of oily sea fish and to reduce their intake of food rich in trans fatty acids. A hospital- and parity-matched control group included 500 pregnant women. Because of the study's size and the fact that the study population had a low rate of preeclampsia, we did not find it relevant to mention in the abstract or in the conclusion that there were no cases of eclampsia or severe preeclampsia in the study group vs 1 case of eclampsia with convulsions and 2 cases of severe preeclampsia in the control group.

A Danish case-control study was undertaken of a cohort of 9434 women.[30] Dietary information was obtained retrospectively from the time period between 6 months and 3 1/2 years after delivery, using a semiquantitative food frequency questionnaire. A control group of 256 women was sampled from the entire cohort. Finally, only 33 questionnaires from preeclamptic women could be included in the analyses (0.35% of the entire cohort) although preeclampsia was probably overdiagnosed (>+ using dip sticks was accepted to define proteinuria). In such a context, no significant association could be demonstrated between fish intake and the risk of preeclampsia.

It is remarkable that the only study that demonstrated highly significant effects of fish oil supplementation on the risk of preeclampsia was conducted in London by the People's League of Health during 1938-9, at a time when the rates of severe "toxemia" were in the region of 6%. This controlled trial was saved from oblivion by S.F. Olsen and N.J.

Secher.[31] The authors randomized 5644 pregnant women to receive or not receive a dietary supplement containing vitamins, minerals, and halibut liver oil from about week 20 of pregnancy. A significant effect of treatment was seen in primiparae, with a 31.1% reduction in the incidence of preeclampsia (95% CI 5-50%, $P = .021$). Interestingly, no significant effect of treatment was seen with regard to the incidence of hypertension in the absence of edema and proteinuria.

Our understanding of preeclampsia also suggests that catalysts for the metabolism of unsaturated fatty acids should be preventive agents. Let us recall that only the precursor in the n-3 family (18:3 n-3) is abundantly provided by the land food chain.

Magnesium,[32] calcium,[33] and zinc[34] are such catalysts and have been explored as preventive agents.

It also makes sense that, in order to prevent preeclampsia, the level of blocking agents of the metabolic pathways must be reduced as much as possible. Alcohol, pure sugar, and trans fatty acids are such blocking agents. A correlation has been established between the intake of trans fatty acids and the risk of preeclampsia.[35] Hormones such as cortisol are also known blocking agents. This can explain how the emotional state of the pregnant woman influences the risk of preeclampsia.[36] It is also theoretically important to avoid

a fast destruction (via peroxidation reactions) of the available long chain fatty acids. The preventive effects of antioxidants are well documented.[37]

As for aspirin (and other antiplatelet drugs), they intervene late in the chain of events (on the ratio of prostacyclin to thromboxane-2). Furthermore, there is a discrepancy between the results of early meta-analyses and later large trials.[38]

Food From the Land and Food From the Sea

In theory, it is easier to meet the specific needs of the developing human brain when the diet includes some food from the sea, because the sea food chain provides preformed and abundant molecules of long-chain fatty acids. The sea food chain has other characteristics. For example, any food from the sea is rich in iodine, a major component of thyroid hormones, which are involved in brain development. Imbalances of thyroid hormones (high ratio of thyroxine [T4] to triiodothyronine [T3]) are associated with preeclampsia and 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. Studies of preeclampsia in the framework of evolutionary medicine are needed.[39] In conclusion, preeclampsia may be understood as the price some human beings must pay for having a large brain when they are more or less separated from the sea food chain.

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