



Deal in the womb: Fetal opiates, parent-offspring conflict, and the future of midwifery

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Summary This paper argues that parent-offspring conflict is mediated by placental β -endorphins in placental mammals, i.e., fetuses make their mothers endorphin-dependent then manipulate them to increase nutrient allocation to the placenta. This hypothesis predicts that: (1) anatomic position of endorphin production should mirror its presumed role in fetal-maternal conflict; (2) endorphin levels should co-vary positively with nutrient carrying capacity of maternal blood system; (3) postpartum psychological symptoms (postpartum blues, depression and psychosis) in humans are side-effects of this mechanism that can be interpreted as endorphin-deprivation symptoms; (4) shortly after parturition, placentophagia could play an adaptive role in decreasing the negative side-effects of fetal manipulation; (5) later, breast-feeding induced endorphin excretion of the maternal pituitary saves mother from further deprivation symptoms. Finally, whatever the molecular mechanism of fetal manipulation is, widespread and intense medical care (such as caesarean section and use of antidepressants) affects the present and future evolution of mother-foetus conflict in the human species (and also in domestic animals) to increase 'fetal aggressiveness' and thus technology-dependency of reproduction.

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Introduction

β -Endorphin (BE) is the human body's feel good and analgesic peptide. It is mostly produced by the hypothalamus and pituitary, however, BE-like forms are also found in the placenta [1]. Placental BE (PBE) is produced since the third month of pregnancy and then its quantity in the maternal plasma

increases steadily until parturition [2]. Its function is not well understood. Parasitic trematodes and nematodes (such as *Schistosoma mansoni*, *Dracunculus medinensis*, *Ascaris suum* and *Trichinella spiralis*) also excrete opiates into the hosts' body to suppress host immune responses [3], suggesting an interpretation that foetuses might also use PBE to suppress maternal immune function [4]. Numan [5] suggested PBE to play a role either in modifying maternal behaviour or in analgesia. Here, we aim to interpret the function of PBE within the context maternal–fetal conflict.

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This conflict is rooted in the difference between the adaptive interest of mother and foetus. Mothers face a negative trade-off between current and future breeding success; since the more nutrients they invest into nourishing a current foetus, the less they can spare for potential future ones. Thus, there must be a maternal optimum of resource-allocation between current and potential future embryos. A maternal optimum is not necessarily optimal for the foetus, or, more precisely, for the genes carried by the foetus. Foetuses might wish to gain more than predicted by their mothers' optimal strategy [6]. Naturally, even the embryo has an interest in conserving some maternal resources for its mother's future survival and reproduction; thus the fetal optimum is still less than the physiological maximum. The parent-offspring conflict simply arises since the fetal optimum of maternal nutrient supply is higher than the maternal optimum.

The adaptive interest of different fetal genes may also differ. Maternally derived alleles tend to share maternal optimum to a higher degree, since copies of the same alleles are more likely (say, 0.5) to be present in potential future siblings. However, paternally derived alleles are less interested in sparing resources for future offspring, since multiple paternity often reduces kinship between them and future half-sibs [7].

Endorphins as fetal tools in the conflict

Hypothesis

Haig [8] already speculated about the likely nature of a hypothetical placental hormone involved in maternal–fetal conflict. Here, we propose the hypothesis that PBE is produced by foetuses to manipulate their mothers' resource-allocation pattern. PBE, like other endogenous opiates, can probably cause addiction and dependency [9,10]. We argue that foetuses make their mothers PBE-dependent and then trade PBE for extra quantities of nutrients. This hypothesis is testable in the sense that it yields in a series of testable predictions. We briefly overview these predictions and summarize the current information about them.

Predictions

1. The anatomic position of PBE production should be in accordance with the view that foetuses produce PBE to manipulate their mothers. The placenta is an organ built of both maternal and fetal tissues. Indeed, the PBE is produced by a fetal tissue in the placenta, more precisely, by the syncytiotrophoblast [11]. This tissue is situated closer to the maternal circulation system than the vast majority of fetal tissues.
2. PBE concentration is predicted to co-vary positively with the nutrient carrying capacity of the maternal circulation system. More specifically, high maternal blood pressure – an important aspect of foetus nutrition according to Haig [12] – is known to come together with high BE levels [13]. Accordingly, hypertensive pregnancies tend to yield in lower perinatal mortality [14], and, at least in case of low pre-pregnancy weight women, also yield in higher birth-weight than normotensive pregnancies [15]. However, an obvious shortcoming of published data on maternal plasma BE levels is that authors did not clarify the origin – i.e., placental versus pituitary – of plasma BE thus these correlations need cautionary interpretation.
3. After giving birth to their babies, mothers may exhibit drug-deprivation symptoms. Indeed, postpartum depression had already been interpreted as an endorphin-deprivation symptom decades before [16].
4. Theoretically, this may be temporarily suppressed by placentophagia, i.e., by eating the placenta. Many mammal species including humans are known to exhibit placentophagia soon after labour [17], and this behaviour is known to have a genetic background at least in rodents [18,19]. Placentophagia may offer a final dose of PBE postponing the rise of symptoms by a day or so. Kristal [20] has already shown that placentophagia is an opioid-driven phenomenon, though he interpreted it within the context of opioid-mediated analgesia. This behaviour has mostly disappeared from modern human societies, thus mothers may face more severe drug-deprivation symptoms. Interestingly, anecdotal information provided by a woman who dared to eat parts of her rough placenta emphasizes the euphoria caused by placentophagia [21].
5. About half a day after parturition, endorphin-dependent mothers may overcome potential endorphin-deprivation symptoms by means of breast-feeding their babies. Breast-feeding is known to promote the release of pituitary endorphins in the mother. These endogenous opiates also participate in the mechanism responsible for the contraceptive role of breast-feeding [22]. Consequently, more intense fetal manipulation will make mothers to breast-feed their babies more intensively and for a

longer period of time. Longer breast-feeding also postpones next conception. This effect is potentially adaptive for the fetal allele provided that it is manifested only when paternally inherited, and that multiple paternity is common [7]. Failure of breast-feeding often comes together – though not always significantly – with a higher chance of postpartum depression, probably due a decline of pituitary BE levels in the plasma [23–25].

6. In case of drug abuse, morphine-dependent mothers are likely to have heavily overloaded endorphin receptors. Their foetuses are predicted to fail to modify maternal resource-allocation patterns by means of PBE. Therefore, morphine-dependent mothers will give birth to low-weight babies and also to face problems in breast-feeding their children. Apparently, this corresponds well to empirical data indicating lower birth-weight and higher neonatal mortality in children of drug positive mothers [26,27]. However, drug-dependency can also decrease maternal capabilities in many other ways, and thus these effects are not specific to opiates.
7. Finally, our hypothesis also predicts that birth-weight should co-vary with postpartum depression positively. However, published data seem to indicate an opposite tendency [28] probably due to other factors – such as severe mood, behaviour, and cognitive symptoms during pregnancy – causing both low birth-weight and postpartum depression [29]. We suggest that birth-weight should co-vary with postpartum depression positively after controlling for confounding effects.

Alternative hypotheses

On the other hand, however, opiates – like PBE – may also suppress maternal immune responses which may yield in an advantage for the foetus. Unfortunately, we do not know whether or not the typical PBE concentration of maternal blood is high enough to exert an immune-suppressive effect. This alternative hypothesis can also explain some of the phenomena mentioned above. On the other hand, it cannot explain, e.g., why maternal blood pressure co-varies with PBE levels.

Similarly, a potential analgesic role for PBE during or after labour [30,20] does not exclude the possibility that it also plays parallel roles in immune suppression and in fetal manipulation of maternal nutrient allocation. However, the analgesic role hypothesis is contradicted by the fact that gestational age does not co-vary with PBE tissue

concentrations, and that PBE content does not differ between placentas collected at elective caesarean section before labour and placentas collected after spontaneous vaginal delivery [11].

Consequently, we cannot exclude the possibility that suppressing maternal immune responses or providing analgesia might have been ancestral functions of fetal BE production in archaic placentals, from which the manipulation of maternal nervous system arose as a new and parallel function.

Fetal–maternal conflict and the future of midwifery

Hypothesis

Whatever the molecular mechanism of the conflict is, mother-foetus counter-interest regarding the allocation of maternal resources exerts a selective pressure upon human beings and other placental mammals. This is a more general – but partially overlapping – working hypothesis than the first one. Considering how selection pressure is modified by human health policies yields in the prediction that fetal aggressiveness – i.e., a particularly strong exploitation of maternal resources by the foetus – will increase in humans.

Prediction

Apparently, rates of pregnancy, delivery and postpartum complications (both somatic and psychological) experienced in advanced societies are high and rising continuously. Among other measures, this is well mirrored by a current increase of the rate of caesarean sections performed in developed societies. Contrary to traditional interpretations widespread in the medical literature [31–34], we interpret this phenomenon as a result of a quick evolutionary response to the change of selection pressure upon the human race. Artificial intervention into the potential costs and benefits of PBE-mediated manipulation affects selective pressures exerted upon humans and promotes adaptation to the new costs and new benefits. We have several reasons to predict that fetal aggressiveness will exhibit further evolutionary increase in response to an improved medical care and health policies in advanced societies.

Firstly, one particular cost of fetal aggressiveness is the increased chance of maternal depression that can jeopardize further maternal care. From the fetal point of view, the optimal degree of manipulation is limited by this effect. In

developed societies, this upper limitation is increasingly eroded by a widespread use of antidepressants, and all other methods of advanced social, economic and medical care that depressed mothers and their babies can rely on.

Secondly, another cost of fetal aggressiveness is the increased birth-weight that can cause delivery complications threatening the survival chances of mother and offspring as well. Human babies are born with an exceptionally high birth-weight as compared to other primates, and any further increase of this is disallowed by the anatomic structure of the human pelvis [35]. However, an increasing dependence on caesarean section as means of delivery can eliminate this limitation too. In developed societies, aggressive foetuses will not necessarily face delivery complications any more.

In a more general sense, both maternal and fetal optimums of nutrient supply are limited by the reduction of postpartum maternal capabilities as a consequence of too high nutrient supply rates during pregnancy. Currently, modern health care and medical practices diminish this limitation as mothers with particularly high nutrient investment into a foetus will suffer a little if any reduction of maternal capabilities and of chances for further reproduction. On the contrary, however, benefits of fetal aggressiveness are not necessarily eliminated in advanced societies.

A persisting advantage of fetal aggressiveness comes with the high birth-weight it is likely to cause. Arguably, high birth-weight babies have a better chance to become healthier, taller and larger-brained and thus cleverer people. Indeed, babies smaller at 3 or 6 months are more likely to develop into pupils having significantly lower scores at high school entrance exams than large bodied ones [36]. Being healthy, clever and tall (more precisely: male body height) is sexually attractive in humans, thus sexual selection favours these traits [37]. Tall men more often have a second family throughout their life and thus tend to gain higher lifetime reproductive success even in modern societies [38].

A further unexpected advantage of fetal aggressiveness may arise in developed societies. The human milk is known to contain natural sedatives that have been claimed to act as maternal tools to sedate infants, and thus to suppress their efforts to overexploit maternal resources [12]. Accepting this view as a working hypothesis, we predict that more aggressive foetuses will be more likely to cause postpartum depression in their mothers that can impede normal breast-feeding. Thus these babies will be more likely to be fed by artificial milk.

These products do not contain psychoactive drugs to suppress infant needs, and also easier to provide in quantities by the parents. Therefore, aggressive foetuses have a higher chance to face no nutrient quantity limitation in the first period of their life. Of course, artificial milk is still inferior to natural human milk in quality; however, this disadvantage is diminishing continuously due to advances in food technology.

Parallel to this phenomenon, developed societies also provide sophisticated obstetrics and gynecology services to domestic animals including placental species. Consequently, cats, dogs, horses, cattle, etc., are also predicted to shift toward larger birth-weights and higher technology-dependency in their reproduction – even if this shift is less pronounced than that of the human race.

Alternative hypotheses

A great number of historical, sociological, clinical, psychological, and even financial factors may also contribute to the current increase of perinatal and postnatal physical and mental complications. At the present moment, we cannot discriminate among these effects and thus we cannot claim that the current increase of these complications are fully explained by our hypothesis.

Concluding remarks

Naturally, we do agree that mothers and babies must receive the best possible health care and medical supply at the current state of science. However, we also point out here that this practice exerts a selective pressure upon our species that favours particularly high nutrient investment into foetuses and thus, indirectly, also favours complicative pregnancies. Mothers (maternal alleles) who supply more to their foetuses will outcompete those who supply less, and babies (fetal alleles) who demand more will outcompete those who demand less. This is a remarkable and potentially quick evolutionary process resulting in an increase of technology-dependency in human reproduction. This implies that we expect to find higher fetal aggressiveness in human populations characterized by more advanced health-care systems throughout more generations. Consequently, PBE levels, (relative) birth-weight, together with endorphin-deprivation psychological symptoms, pregnancy induced hypertension, and caesarean section rates are predicted to rise continuously in technically advanced human societies.

Briefly, we argued above that PBE is the particular hormone that fetuses use to manipulate maternal behaviour during the parent-offspring conflict in placental mammals including humans; and we predicted that current and future evolution of human reproductive behaviour is likely to become more technology-dependent due to indirect selection pressure exerted by advanced medical care. Admittedly, the hard data supporting our views are scarce at the present moment, however, we do hope that future research efforts will either prove or falsify our arguments.

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