Fetal adaptation to stress
Part I: acceleration of fetal maturation and earlier birth triggered by placental insufficiency in humans

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Abstract

This review is an attempt to provide an integrative view for the biological changes triggered by fetal stress through a multidisciplinary approach. Acceleration of brain and lung maturation in certain risk pregnancies was first described clinically and confirmed by biochemical, electrophysiological and experimental data. Moreover, new experimental findings suggest that a fetal clock centrally mediated by fetal nutritional status could determine timing of parturition. However, some skepticism persisted about the usefulness of this body of knowledge for obstetrical management in developed countries. The interest concerning this adaptation to intrauterine stress was later renewed from various sources, as developed in Part II.

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1. Introduction

Fetal stress has been a hot topic for decades, an important issue for both obstetricians and neonatologists in the peripartum management of the mother and infant. It has

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become clear recently that the effects of fetal stress, both short term and long term, both beneficial and adverse, are not only of interest for perinatology but also for evolutionary biology, for neurology and for adult medicine. This general review represents an attempt to bring together data from several disciplines, including authors from obstetrics, pediatric neurology, pediatric pulmonology and animal biology.

This review is presented in two parts: clinical data will be discussed in Part I: acceleration of maturation may occur in brain and lungs, as an adaptation to fetal stress. Early initiation of parturition may also be associated. These adaptive changes could represent a life-saving answer to moderate stress with resultant earlier birth of a more mature newborn, and increased survival as long as the unfavorable fetal environment is not too early or too severe.

Evolutionary aspects, experimental and epidemiological data on adult health will be discussed in Part II. The capacity to vary development in response to the environment is demonstrated in amphibians, in which the neuroendocrine stress system has been studied, with corticotropin releasing hormone as the primary player. Adverse long-term effects on hippocampal neurons have been studied in rats, as a consequence of prenatal stress. Finally, a new field of investigation opened in the 1990s with the Barker hypothesis, suggesting long-term effects of fetal undernutrition on the determination of chronic adult diseases.

2. Historical view

2.1. Possible fetal adaptation to unfavorable circumstances

Questioning the so-called clockwork precision in fetal maturation was not politically correct in the 1960s as clinical dating in neonates relied on this postulated precision and has been accepted for 20 years. Some doubts however arose about the immutability of developmental processes with precise documentation of ovulation based on temperature curves and later by pregnancies obtained by stimulation of ovulation.

The first break in this dogma was the discovery by Gluck and Kulovich in 1973 [1], using the biochemical assessment of lung maturation by lecithin–sphingomyelin (L/S) ratio, that both brain and lung maturation may be accelerated in some stressed pregnancies. Further clinical data in 1973 and 1977 [2,3] supported this finding. Undernourishment seems to be the common factor in preeclampsia, multiple birth and uterine malformation. As reviewed by this author [4–6], in some human fetuses with placental insufficiency or multiple pregnancy, acceleration of maturation may occur in brain and lungs, as an adaptation to stress. Moreover, accelerated maturation is associated with earlier initiation of parturition. Intra uterine growth retardation (IUGR) in itself may be considered as part of the adaptive response [7]. However, clinical evidence concerning acceleration of brain maturation was still considered too subjective and no consensus was obtained at this time concerning those adaptive changes.

2.2. Confirmation based on electrophysiological data

Electrophysiological confirmation came in 1985 with data on brain auditory evoked responses (BAERs) in IUGR newborn infants [8], demonstrating that conduction is
accelerated through the brainstem. Shortening of visual evoked potential latencies has also been demonstrated [9] indicating an advance of maturation of the primary visual cortex in this population. Experimental data at this time were scarce; the first confirmation came with experimental IUGR in rats [10]: an acceleration of maturation based on biochemical data, mainly located in the brainstem structures, is concomittent with an adverse effect in cerebral hemispheres, particularly in the hippocampus. Recent experimental data will be described in Part II.

2.3. Resistance to the concept of fetal adaptation

Curiously the suggestion that environmental stress may be favorable, at least for immediate survival, in certain categories of risk pregnancy does not seem «natural»; the clock-work precision of genetically determined programs appears more reassuring than flexibility determined by the environment. As a consequence, attempts to refute this flexibility came from various fields: (1) in neurology, the reality of a beneficial effect has been refuted in a study based on neonates born after chronic fetal distress whose motor behavior was impaired at birth [11]. The reason for these negative results probably lies in acute distress experienced during the days immediately preceding birth: in the above mentioned study most of the neonates were born after emergency cesarean section for fetal distress. In the Amiel-Tison study [3], in contrast, most of the neonates were born without signs of fetal distress. Since then umbilical and cerebral Doppler velocimetry has helped to clarify the debate with the identification of two successive periods in the compromised fetus. At first, compensatory mechanisms are at work and fetal acceleration of maturation may be observed; later, compensatory mechanisms are overwhelmed, signs of fetal distress are present and may lead to hypoxic–ischemic brain damage. In these last cases, acceleration, if any, may be masked by pathological neurological signs. (2) In obstetrics, the probable acceleration of lung maturation was used during the 1980s to advocate very early cesarean section (CS) (as early as 23 to 24 weeks of gestation) in pregnancies with severe IUGR; the high rate of respiratory distress syndrome (RDS) and mortality in this population has been considered as contradicting the existence of adaptive changes. This debate and consequent warnings came at a time when the notion of a threshold below which no fetal adaptation could be expected was not yet established. (3) In epidemiology, the following statement [12] is an example of the pitfalls due to non-identification of the two successive phases in compromised fetuses: «Given that preeclampsia is a major cause of IUGR, which is the most important risk factor of cerebral palsy (CP), it appears biologically implausible that pre-eclampsia would protect against CP». Identical considerations concerning the increased risk of CP observed in twins and triplets have been added to this apparently «common sense» statement. This epidemiological approach seems to justify skepticism concerning the potential benefits of undernourishment to the developing fetus. By contrast, recent data in multiple pregnancies [13] (Papiernik E and Kogan M, unpublished data) tends to demonstrate a reduction in perinatal mortality when obstetrical management takes into account presumed adaptive changes secondary to undernourishment. The central question in this matter has been elegantly posed under this title by Collins and Paneth [14]: «Could preeclampsia
be causative of CP under some conditions, and protective under others? The answer is yes; as an example, the association of preeclampsia with reduced incidence of intraventricular hemorrhage (IVH) in preterm infants [15,16] suggests a protective effect.

3. Acceleration of brain maturation

3.1. Neurological assessment of maturation: methodological issues

Neurological assessment of maturation from 28 to 40 weeks gestation was initiated by Saint-Anne-Dargassies [17,18] and later used and modified in various ways. The personal goal of one of us (Amiel-Tison) has been to select the most useful neurological criteria and to describe and illustrate the infant responses to make the exam both more appealing to clinicians and more reliable [19]. Additional simplification has resulted in a 10-item table (Table 1) [20,21]. The originality of this approach essentially lies in the description of maturative stages at 2-week intervals, as initially proposed by Saint-Anne-Dargassies. According to this system, between 32 and 40 weeks, a definition of the «neurological age» can be reached when most of the responses correspond to the same 2-week gestational period; the pattern is designed as “uniform” when seven or more results are in the same age interval. When more than three responses are off the line, in other words when responses are scattered all over, the pattern is designated as “scattered” and no firm conclusion on a “neurological age” can be obtained.

From our experience with this method, several situations can be described in the neonatal period, as represented Table 2. When the neonate is in fairly good condition, acceleration of maturation may be identified since birth, based on a uniform pattern (II.A). In some cases, the scattered pattern observed in the first days becomes uniform by the end of the first week, when general condition improves with adequate postnatal care (II.B). In rare cases however, the initial scattered pattern persists in the following weeks (II.C). This is often due to poor suck and poor active tone performances, contrasting with the other criteria. Such a situation may be indicating brain dysfunction.

The temptation of scoring systems for gestational staging has not been resisted however, usually combining neurological criteria to physical criteria derived from Farr [22]. The most popular scoring systems are the Dubowitz [23,24] and the Ballard [25]. It certainly is gratifying to obtain in 100% of the cases a number defining maturation. However, on one hand, it suggests a level of accuracy which does not really exist in these dynamic systems. On the other hand, we think that it is a deprivation for clinicians not to be able to integrate the clinical data in the overall interpretation of each case. Moreover, scores are generally applied within the first hours after birth (and not repeated), at a time when the general condition of the neonate is grossly interfering with performance (mainly with sucking and active tone). Therefore the total score in many cases will be lower than it should be. This pitfall is probably responsible for a marked underestimation of adaptative phenomena.
Table 1
Neurologic criteria described at 2-week intervals from 32 to 40 weeks of gestation, without scoring

<table>
<thead>
<tr>
<th>Weeks gestation</th>
<th>Below 32</th>
<th>32–33</th>
<th>34–35</th>
<th>36–37</th>
<th>38–39</th>
<th>40–41</th>
</tr>
</thead>
<tbody>
<tr>
<td>POPLITEAL ANGLE</td>
<td>130° or more</td>
<td>120°–110°</td>
<td>110°–100°</td>
<td>100°–90°</td>
<td>90°</td>
<td>90° or less</td>
</tr>
<tr>
<td>SCARF SION</td>
<td>no resistance</td>
<td>very week resistance</td>
<td>largely passes midline</td>
<td>slightly passes midline</td>
<td>does not reach midline</td>
<td>very tight</td>
</tr>
<tr>
<td>RETURN TO FLEXION OF FOREARMS</td>
<td>posture in extension most of the time</td>
<td>weak or absent</td>
<td>present, less than 4 times</td>
<td>4 times or more but inhibited</td>
<td>4 times or more not inhibited</td>
<td></td>
</tr>
<tr>
<td>FINGER GRASP</td>
<td>present</td>
<td>absent</td>
<td>present</td>
<td>present</td>
<td>present</td>
<td>present</td>
</tr>
<tr>
<td>RESPONSE TO TRACTION</td>
<td>very week or absent</td>
<td>able to lift part of the body weight</td>
<td>able to lift all body weight for 1 sec</td>
<td>complete righting for a few secs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RIGHTING REACTION lower limbs and trunk</td>
<td>no support</td>
<td>brief support lower limbs only</td>
<td>begins to maintain trunk</td>
<td>trunk more firm</td>
<td>begins to raise head</td>
<td></td>
</tr>
<tr>
<td>RAISE-TO-SIT (neck flexor muscles)</td>
<td>no movement of the head forwards</td>
<td>face view head rolls on the shoulder</td>
<td>passes briskly in the axis</td>
<td>more powerful</td>
<td>perfect, minimal lag</td>
<td></td>
</tr>
<tr>
<td>BACK-TO- LYING (neck extensor muscles)</td>
<td>no movement of the head backwards</td>
<td>head begins to lift but cannot pass backwards</td>
<td>passes briskly in the axis</td>
<td>powerful movement backwards</td>
<td>perfect, minimal lag</td>
<td></td>
</tr>
<tr>
<td>CROSSED EXTENSION</td>
<td>good extension but no adduction</td>
<td>tendency to adduction</td>
<td>reaches the stimulated foot</td>
<td>crosses immediately</td>
<td></td>
<td></td>
</tr>
<tr>
<td>*SUCKING</td>
<td>1°/sec negative pressure Interburst time</td>
<td>3 or less</td>
<td>4 to 7</td>
<td>8 or more</td>
<td>idem</td>
<td>idem</td>
</tr>
<tr>
<td>*FOOT DORSIFLEXION ANGLE</td>
<td>≥ 50°</td>
<td>40°–30°</td>
<td>70°–10°</td>
<td>mal</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Periods of rapid modification are highlighted, indicating the most discriminative period for each observation. Asterisk indicates that the items are not appropriate for maturational assessment performed after several weeks of postnatal life: sucking is modified as a result of practice; the foot dorsiflexion angle remains as it was at the time of premature birth (from Ref. [20], with permission).
3.2. Clinical characteristics and uncertainties

In our first description [3], an advance in neurologic maturation was detected in 16 infants with GA between 30 and 37 weeks; an advance of 4 weeks or more was chosen to define neurological acceleration, in order to be outside the 95% confidence limits; during the study period however, an equal number of neonates had signs of advanced neurologic maturation of 2 to 3 weeks. Therefore the phenomenon of advanced maturation did not appear as an all or none phenomenon but rather a progressive response of variable degree. Moreover, neurological acceleration was not restricted to IUGR fetuses: in the cohort of 16 neonates with an advance of 4 weeks, only three of them had a birth weight (BW) below the 10th centile on the Lubchenco growth curve, and 13 had a BW between the 10th and the 50th. So the tendency for growth insufficiency was there, but not extreme; i.e. all these fetuses were possibly growth restricted in the sense that, due to shortage of nutrients, they did not achieve their genetic growth potential [26]. Similar results have been obtained in a cohort of twins: the same proportion of advanced neurological and physical maturation was found in both IUGR and non-IUGR neonates [27].

The occurrence of advanced maturation earlier than 30 weeks is unknown; due to fragility of very premature neonates, the method described above cannot be applied. Therefore the existence of a threshold cannot be explored clinically.

The pervasiveness of the effect of fetal stress on cerebral function also cannot be evaluated on clinical grounds: After 40 weeks GA, the evolution of tone and reflexes is not rapid enough to detect an advance of a few weeks.

Only a few studies concern behavioral changes associated with neurological acceleration of maturation. The frequent observation of a state of hyperalertness (based on fix and track and social interaction) is puzzling; but in light of experimental findings, this hyperalertness could possibly be related to high concentration of corticotropin-releasing hormone (CRH) (see Part II). An impaired fetal responsivity to novelty in fetuses of mothers with high CRH (ability depending on areas of the fetal brain rich in CRH receptors, such as parahippocampal regions) has been observed [28], possibly due to neurotoxicity of stress hormones during critical periods of development (see Part II). A few studies in VLBW infants suggest that a selective impairment of memory could be the explanation for the high incidence of learning disabilities observed in this population, even in the group considered neurologically normal. Isaacs et al. [29] tested

<table>
<thead>
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<tr>
<td>Identification of three courses in the neonatal period, based on 10 neurological criteria described at 2-week intervals</td>
</tr>
<tr>
<td>Pattern within the two first days of life</td>
</tr>
<tr>
<td>(A) Uniform, advanced</td>
</tr>
<tr>
<td>(B) Scattered</td>
</tr>
<tr>
<td>(C) Scattered</td>
</tr>
</tbody>
</table>

(A) Acceleration of maturation based on a uniform pattern since birth. (B) Delayed uniform pattern, when general condition improves. (C) Persisting scattered pattern as an early clue to brain dysfunction.
everyday memory in correlation with neuroimaging in VLBW infants; they found an
association between smaller hippocampal volumes and deficits in certain aspects of
every day memory.

4. Acceleration of lung maturation

4.1. Are adaptive changes observed in the lung?

During the 1970s and 1980s, a low incidence of respiratory distress syndrome
(RDS) in neonates having experienced a shortage of nutrients such as in multiple
pregnancies for instance [5] was observed. Within this period, biological observations
tend to show that the L/S ratio in amniotic fluid was reaching mature levels earlier in
maternal hypertensive pregnancies [30] as well as in twin pregnancies [31], therefore
tending to demonstrate an accelerated fetal lung maturation (FLM). This accelerated
FLM could be related to an increase in plasma cortisol level [32], a known stimulus of
FLM. It is necessary to remember that in the 1960s and 1970s, most infants admitted
to the NICU, had a gestational age of 32 weeks or more, and were born after a
spontaneous premature birth (the very sick ones died in utero). In this population
therefore, adaptive changes could take place, as suggested by a lower incidence of
RDS.

Later, most infants admitted to NICUs had a gestational age of 31 weeks or less, a
higher incidence of RDS with a high proportion of them being born after CS for fetal
distress. The postnatal course was jeopardized in many ways. As a consequence,
accelerated FLM in IUGR newborns has been seriously questioned. In fact, the data in
the 1990s, based on better controlled studies, with comparison based on gestational age
(GA) tend to show an identical or even an increased incidence of RDS in small-for-
gestational-age (SGA) compared to appropriate-for-gestational-age (AGA) infants. The
study of Pena et al. [33] matched 35 premature SGA with two groups of premature either
with similar weight or with similar GA (mean GA 30.8, mean BW 1000 g). The
comparison by weight showed a similar incidence of RDS in SGA, 42% vs. 48%; when
the comparison was based on GA, an increased incidence was observed in SGA (65%) vs.
in AGA (40%); the difference was not significant due to the small cohort.

The study by Tyson et al. [34] performed on a large population showed that SGA
infants had a significantly increased risk of RDS at every GA between 27 and 38 weeks.
These results have been confirmed by other authors, at least in the low GA group [34–38].
The study of Bernstein et al. [38], including 19,759 neonates with a GA between 25 and
30 weeks, showed a significant association of IUGR with RDS. For twins, IUGR at any
GA was associated with a higher proportion of adverse outcome in several studies [39–
41]. Finally, one study [35] found an age-dependent aspect of these results, i.e. the GA
above which FLM could occur. In this study, between 25 and 28 w GA, the SGA-group
compared to AGA had a longer need for ventilator treatment due to RDS; but between 29
and 32 w GA, RDS incidence was lower in the SGA group.

Biological assessment of FLM does not support these epidemiological data: from
the following studies the timing of FLM seems to be similar in SGA and AGA
fetuses, whatever the cause of IUGR, either maternal hypertension or other causes. Schiff et al. [42] did not observe any difference in a study of FLM dealing with preeclamptic pregnancies; Winn et al. [43] observed similar FLM when assessed by the L/S ratio in twin and in singleton pregnancies. However, based on biochemical assessments in amniotic fluid, one study [44] shows a definite trend for FLM acceleration after 32 weeks, albeit not statistically documented.

4.2. Experimental data and possible mechanisms involved

Experimental data however support the possibility of an accelerated FLM in stressed pregnancies. Studies on sheep undergoing long-term hypoxemia after placental embolization showed an increase in fetal plasma cortisol, preceded by a peak of adrenocorticotropic hormone [45]. In the same experiment, a significant increase in fetal lung surfactant associated proteins (SP) was observed [46], a 2.7-fold increase in fetal lung SP-A mRNA and a 3.2-fold increase in SP-B mRNA in the embolized group compared to the control group, suggesting an enhancement of FLM. This finding was associated with a significant decrease in total lung DNA content, which is consistent with a switch from fetal lung cell division to cell maturation due to an increase in fetal plasma cortisol. Whether this switch is more deleterious in very young fetuses than later could provide an explanation to contradictory data discussed above in human neonates and support the notion of a threshold for adaptive changes.

5. Earlier birth

5.1. Epidemiological data on gestational age distribution

5.1.1. Natural history in pregnancy induced hypertension

It is necessary to go back to the natural history of preeclampsia, before modern management modified its spontaneous evolution; this means back to the 1960s, a time when the disease was well described but the therapeutic approach timid, when early CS for fetal rescue was not performed. Based on the Cleveland survey (1962–1968) [47] toxemic patients have a tendency to deliver earlier, as shown in Fig. 1, when comparing the birth frequency distribution for all primigravidae with that of primigravidae with significant preeclampsia.

5.1.2. Natural history in multiple pregnancy

The natural history is again to be found in data from the 1960s, as reviewed by Mc Gillivray [48], establishing the tendency for premature labour to occur in multiple pregnancy. Most recent data from the United States [49] establish the percentage distribution by GA for singleton, twin and triplet live births (Fig. 2). Marked differences in length of gestation among these groups are striking, 3 weeks shorter in twins, 6 weeks shorter in triplets. As repeatedly shown in twins, a downturn in BW is evident [49], beginning by 28–30 weeks and earlier in triplets by 27–28 weeks.
5.2. Hypothetic cascade in humans, ending in premature birth

The secretion by the placenta of CRH increases during human pregnancy and reaches maximal values around the onset of labour. A relationship between maternal plasma CRH and preterm delivery has been described [50], and the concept of a «CRH placental clock», which could be active from the early stages of human pregnancy and could determine timing of parturition and then length of gestation, has been proposed [51].

There is some evidence [52,53] that in the event of intrauterine infection or hypoxia, the placenta increases its CRH production. However, the mechanisms of action of CRH remain obscure. The presence of functional CRH receptors in the myometrium [52,54] suggests that CRH could play a central role in coordinating the myometrial transition from a state of relaxation during pregnancy to one of contraction at the onset of term or preterm labour.

During pregnancy, CRH receptors are linked to several intracellular pathways via G-proteins. Their activation by CRH seems to lead to the production of cAMP, cGMP and NO, which are potent myometrial relaxants.
At the onset of term or preterm labour, the upregulation of oxytocin receptors results in a PKC-induced switch to low affinity state of the CRH receptors leading to a decrease in intracellular cAMP, facilitating the actions of uterotonic compounds: oxytocin and prostaglandins [55]. However, this interesting hypothesis is far from being proven. CRH level has a low predictive value for preterm labour if applied as an isolated measure in a low-risk population [56]. CRH alone does not induce contractility in human myometrium in vitro and the hypotheses dealing with CRH are based only on correlations and not on demonstration of a direct causal effect upon the onset of labour.

Recent experimental data on fetal sheep [57] open a new field of investigations in showing a correlation between nutritional status in late fetal life (and therefore fetal leptin) and fetal HPA activity; these findings suggest a “fetal clock” centrally mediated by fetal nutritional status.

6. Conclusion

Conceptually new in the early 1970s, fetal adaptation to stress is now relying on various experimental data. However, uncertainties concerning a probable threshold (a GA below which adaptation does not occur) and the lack of biological criteria available during pregnancy are still responsible for skepticism about the usefulness of this body of knowledge for obstetrical management.

Since long ago, pediatricians were aware of remarkable survival in very preterm and very thin neonates who manage to breathe and suck without help. It still is the case in
developing countries where many IUGR neonates, when lucky enough to avoid death in utero, benefit from the short-term favorable effect of stress on survival: they do not need intensive care, even at low GA, as long as fetal stress has not operated too early in pregnancy or been too severe.

In developed countries by contrast, with the dazzling advances in perinatal care, these adaptive changes, if any, no longer influence the rate of survival in NICUs; as a consequence, adverse long-term effects on cerebral function (memory and learning problems) have a tendency to blur the potential beneficial effects. We have to admit that these adaptive changes, such as they are, do not mean that such stressed pregnancies create an enviable situation for the fetus when compared to normal intrauterine growth, typical schedule of maturation and timely birth.

References


