Review paper

Fetal sensory competencies

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Received 14 February 1996; accepted 7 June 1996

Abstract

A growing body of evidence is available about the functioning of fetal sensory systems during gestation. This article aims at reviewing data concerning (i) the presence of potential sensory stimulation in the fetal milieu, (ii) the sequential functional development of the sensory systems and (iii) physiological and behavioral responses of fetuses to various types of stimulation. Human data are compared with data collected in other mammalian species. Most studies have investigated auditory and chemosensory (olfactory and gustatory) responsiveness of the fetus in the second half of gestation. They demonstrate that (i) motor and heart rate responsiveness depends on gestational age and characteristics of stimulation; (ii) fetal sensory experience has short- and long-term effects at morphological, functional and behavioral levels (for example transnatal learning). The clinical consequences of the fetal sensory functioning are developed.

Keywords: Fetus; Sensory functioning; Vestibular system; Somesthetic system; Olfaction; Gustation; Audition; Vision; Fetal learning; Behavioral states

1. Introduction

Research on fetal sensory development can be seen from a medical point of view as the result of a scientific intrusion performed by experimental zoologists and psychologists into the domain of obstetricians. Indeed, the first systematic attempts at analyzing fetal responses to direct sensory stimulation have been conducted in the auditory domain by obstetricians, long before psychologists became interested in this question (see below). These obstetricians had a pioneering attitude at a time where the dominant opinion was that the fetus lived isolated from the agitation of the world. But, these obstetricians were 'supported' by the vast cohort of pregnant women who had for a long time performed their own observations. They had noticed that, since mid-gestation, they could feel the baby they carried jerk in the womb when a loud noise occurred in their vicinity.

During the first half of the XXth century, developmental psychologists demonstrated that the sensory systems of the newborn function at a quite good level of performance. Since it does not seem plausible that this sensory functioning has a sudden inception at birth, this observation raised the question concerning prenatal development and functioning of the sensory systems.

The development of ultrasound techniques in the seventies (cardiotocography, real-time ultrasonography) allowing the observation of fetal behavior, made possible investigations of fetal responsiveness to sensory stimulation. Today obstetricians and developmental psychologists, although inspired by different motives (development of diagnostic tools for the former, extension of knowledge about psychobiological development for the latter) often work in collaborative programs to better describe the ontogeny of fetal sensations and perceptions.

This in utero fetal functioning requires that: (i) there are potential sources of stimulation in the fetal milieu,
and (ii) the sensory systems are functional, thus mature enough, at both peripheral and central levels. Thus, in the first section of this paper, the fulfilment of these requirements plus the presentation of evidence of fetal functioning are presented for each sensory system. In the review of available data we will follow — except for the vestibular system which will be included among the proprioceptive-somesthetic sensitivities — the developmental sequence demonstrated in comparative anatomical studies performed in the human species and other vertebrates. These studies showed that sensory systems do initiate their maturation according to the following sequence: somesthetic system, chemosensory systems (olfaction and gustation), vestibular system, auditory system and visual system. In the last section, the consequences (i) for the fetus and (ii) for the newborn of fetal sensory experiences are considered in the chemosensory and auditory modalities.

2. Fetal sensory functioning

2.1. Somesthetic and proprioceptive systems

2.1.1. Potential sources of stimulation

Somesthetic and vestibular systems are stimulated in-separably in most occurrences of fetal life, especially by fetal and maternal movements. It is quite impossible to determine to what extent each system contributes to an observed response. While the amniotic fluid should cushion the impact of fast maternal motions, the fetus is exposed to an increasing number of contacts and displacements as gestation proceeds. There are contacts with the uterine wall, contacts between hands and body, hands and face hands and mouth [1]. This last type of contact may induce sucking behavior as it can be frequently seen by ultrasonographists.

2.1.2. Structural development of sensory transducers

Somesthetic system. The somesthetic system develops according to a cephalo-caudal pattern. Neuronal free ending receptors can be found in the mouth and in the peri-buccal zone as soon as 8–9 weeks GA (gestational age). Meissner and Pacini corpuscles develop soon after. Tactile receptors are to be found on the face, the palm of the hands and the sole of the feet by 11 weeks. By the 15th week they are found on the trunk and proximal zones of arms and legs and on the whole skin by the 2nd week [2]. Their density, especially for the free-ending nerves is greater than in the adult.

Vestibular system. By the 5th week, the otic vesicle divides in two parts that will become the saccula and the utricula. The semi-circular canals stem out of the utricula by the 6th week. On purely morphological criteria the vestibular apparatus is mature by 14 weeks. Afferent connections from the vestibular nerve, starting well before neuroepithelium differentiation is ended, stimulate its development.

2.1.3. Evidence of fetal sensory functioning

Somesthetic system. Several clinical interventions including a tactile component, and performed during labor, evoke a significant heart rate acceleration in most end of gestation fetuses. This has been found during: fetal scalp blood sampling [3], a 15-s manual pressure on the scalp [4] and intra-amniotic injection of fluid through a pressure measurement tube [5]. The only other source of data is the observations performed by Hooker [6] and Humphrey [7,8] on non-viable aborted fetuses during their short extra uterine life in a hot saline solution. These perinates respond through a movement to a calibrated light touch to the upper lip as soon as the end of the 7th week, when nerve endings have not yet reached the dermis thus suggesting that the neural plexus function like specific receptors. The whole body surface — except for the back of the trunk and the top of the head, is responsive to touch stimuli by the 13–14th week. Deep pressures manually exerted on the fetal body through maternal abdominal tissues or vigorous shaking of the uterus evoke large heart rate accelerations that can be accompanied with motor responses [9,10]. Pressure at fetal head level may evoke accelerations [11] as well as decelerations [12]. A flush of cold water (4°C) on the fetal face during labor induces a motor response and a HR (heart rate) increase even when given during a quiet sleep episode (a poorly responsive state) [13].

Nociceptive stimulation. Apart from the HR changes induced by scalp blood sampling, and the startles evoked by contacts with the needle during amniotic fluid sampling, very little is known about fetal responses to nociceptive stimulation. It has been shown that endogenous opiates β-endorphin and β-lipotropin blood concentrations are higher after a breech delivery or a vacuum delivery than after an eutocic and thus supposed less stressful delivery [14].

Vestibular system. Premature babies start showing Moro-like responses by the 25th week, a response that has been described earlier by Hooker [6]. Elliot and Elliot [15] suggested that during the 5th month, the fetus starts to orient itself in utero with a kicking-like behavior. Fetus self-orientation has been discussed in relation to the birth position [16]. A concurrent hypothesis, suggesting the functioning of a central mechanism suppressing vestibular responsiveness, has been raised [17]. This mechanism would prevent the fetus from responding to every maternal motion. Recent data from our group demonstrate that, by the end of gestation, fetuses display HR changes in response to maternal passive rocking and swaying, the nature and the amplitude of the change depending on the duration of the motion [18].
2.2. Chemosensory systems (olfaction and gustation)

2.2.1. Potential sources of stimulation

The amniotic fluid is the most obvious mediation of potential chemical stimulation. The fraction of this fluid which is in contact with the oral and nasal chemical receptors is continuously replaced due to frequent inhaling and swallowing bursts. These receptors might also be stimulated by fragrant molecules that have entered the fetal blood stream. Such molecules may pass from the blood vessels which irrigate the chemoreceptors [19]. Although often hypothesized, this activation mode has not yet been demonstrated in the fetus.

The amniotic fluid carries a large number of fragrant substances [20]. Its composition shows daily variations depending on fetal micturition and maternal food intake. Animal studies have demonstrated that olfactory substances which have not been metabolized at maternal, placental or fetal levels can be found in the amniotic fluid [21]. An increase in placental permeability during gestation might raise the level of this transfer of dietary substances [20]. Its composition shows daily variations not yet been demonstrated in the fetus.

2.2.2. Structural development of sensory transducers

Oral chemoreception. Oral chemoreception is both tacto-chemical via trigeminal nerve and specifically gustatory through the activation of taste buds. These buds can be found as early as 12 weeks and are morphologically mature by 13 weeks [23]. They are displayed all over the oral cavity at first and then concentrate and, at birth, remain mainly on the tongue and on the anterior hard and soft palate [23,24].

Nasal chemoreception. Nasal chemoreception is performed by three systems whose respective contributions to the olfactory system remain unclear. The main olfactory subsystem, which in aerial conditions detects weak stimulation, shows adult-like ciliated neuroreceptors by the 11th week. The intra-nasal trigeminal nerve endings, which — in air — mostly respond to strong stimulation including a tactile (the freshness of menthol) or an irritating component (the prickling sensation of ammoniac), appear by the 4th week and respond to stimulation by the 7th week. The third system, named the accessory olfactive system and composed at the periphery by the vomeronasal organ, initiates its development by 5–8 weeks and reaches its maximum development at the central level by the 20th week. For some embryologists it is considered that, by this time, it starts to decline at a variable rate depending on individual patterns [25]. However, recent data indicate that it subsists in most adults [26] in whom it has been shown to be activated by specific compounds [27]. The fetal responsiveness of this organ is still unknown.

2.2.3. Evidence of fetal sensory functioning

Oral chemoreception. Behavioral data on fetal gustation are weak and inconsistent. Injection of a saccharine solution into the amniotic fluid of chronic hydramnios gestations led to a reduction of the maternal abdominal volume that was attributed to ingestion of the fluid by the fetus [28]. However, spontaneous fluctuations of the amniotic volume in this syndrome render this conclusion suspect, since two fetuses observed in similar conditions seemed to increase as well as decrease their swallowing [29]. It should however be noted that intra-amniotic injection of a bitter solution can reduce fetal swallowing [29]. Electrophysiological recordings in the sheep have established that gustatory receptors are clearly functional in utero. The responses to various stimulation are similar for the fetus, the newborn lamb or the adult sheep [30,31]. They become larger and stable with gestational age. Although a large inter-individual variability was seen, responsiveness to acid and bitter stimulation seems to be elicitable earlier than to salty stimulation [23].

Nasal chemoreception. By the third trimester of gestation all chemosensory systems of the nose seem ready to be functional: the nostrils have become patent and let potential stimulation born by the amniotic fluid be inhaled. At the moment, there is no direct evidence of fetal olfaction in the human species. However, such responses have been demonstrated in the 6th month premature babies and similar performances may be inferred in fetuses of equivalent gestational age (GA) [20]. They become stable by 7–8 months GA. Fetal responsiveness to chemical stimuli has however been demonstrated in the rat and in the sheep. In the sheep, for example, intranasal injections of odorant components induce important HR changes in the fetal sheep, while a control solution has no such effect [32].

2.3. Auditory system

2.3.1. Potential sources of stimulation

The fetal sound environment. The first series of human intra-abdominal recordings was performed using microphones covered with rubber membranes which were inserted (i) in the vagina or the cervix nearest to the uterus in either pregnant [33–35] or non-pregnant women [34,36,37], or (ii) inside the amniotic cavity after rupture of the membranes during or after delivery [34,35,38,39]. Except for the acoustic band analysis of Murooka et al. [35] and Busnel [37], only global measurements were performed in these studies. On the whole, they described a very noisy womb (72–96 dB SPL, ref.: 20 μPa) with only very loud external low frequency sounds being transmitted to the amniotic fluid. The considerable background noise was interpreted as originating from te maternal cardio-vascular system. However, some authors recorded significantly lower
sound pressure levels (SPLs between 30 and 50 dB) in non-pregnant women or after delivery [33,35].

**Maternal background noise.** In contrast to the findings from the initial studies, the more recent ones using hydrophones, adapted to fluid impedance, and narrow band analysis have indicated that the womb is a relatively quiet place. When the mother is in a calm environment and when there are no abdominal gurgles which clearly emerge with high SPLs from the background noise, the mean SPLs are comparable to those generally encountered externally [40–43]. The recorded intra-uterine background noise is a composite of: (a) electronic noises from the hydrophone and amplifiers, (b) ambient external noises and (c) various biological maternal and fetal noises (respiratory, movements, gastrointestinal, cardio-vascular, laryngeal); it is mainly composed of low frequencies under 500–700 Hz. Pressure levels show a regular and significant decrease as frequency rises. Frequency band analyses have demonstrated that the important global pressure levels previously obtained were due to infra-sounds (Benzaquen et al. [43] and Gagnon et al. [44] measured 85–97 dB at 12.5 Hz) and/or very low frequencies below 50–60 Hz [43,45] for which human absolute auditory thresholds are very high. Peters et al. [46] clearly showed that this high energy peak represents resonance from the buildings in which the recordings were made. Therefore, contrary to long-held opinion, this high energy does not have a biological origin.

Low-pitched pulsation recorded at frequencies above 50–60 Hz and under 500–700 Hz, and interpreted as vascular sounds, were identified either as the maternal heart-beat [34,35,47], the umbilical artery [42], the uterine artery [33], or utero-placental blood flow [40,43,45]. All the recent data suggest that vascular sounds, occasionally present in the recordings, are not always present at the same sound pressure level everywhere inside the human amniotic cavity. For instance, during delivery, Benzaquen et al. [43] were able to record maternal cardio-vascular sounds at the fetal neck level in only two out of 10 mothers and never during uterine contractions. This was interpreted to mean that the sounds were of utero-placental — not maternal — origin. When these pulsating noises could be recorded, their emergence from the background noise was of only 19 dB SPL at 100 Hz and 2 dB SPL at 650 Hz.

Power spectrum analysis shows that when considering intra-uterine components at or above 100 Hz, various values are found as a result of different transducers (best sensitivity in the low or in the high frequencies) and recording sites. Querleu et al. [40,47], after several series of recordings far from or close to the placenta with different transducers, measured mean SPLs from 65 to 28 dB SPL, the lowest value being obtained far from the placenta with only 20 dB SPL at 500 Hz and no more than 10 dB PL at and above 700 Hz; an overall 25 dB SPL emergence of the maternal heart-beat was found. The authors suggested that noises from the placenta probably have a higher masking effect than cardiac noise. Gagnon et al. [44] with another type of hydrophone located in a pocket of fluid near the fetal neck and, therefore, far from the placenta, measured 60 dB SPL at 100 Hz with less than 40 dB above 200 Hz. Thus, it now seems clear that the contribution of vascular sounds to the recorded background noise depends on the location of the transducer.

**In utero attenuation of auditory stimuli.** The most recent band analysis on the attenuation of airborne broad- and narrow-band noises and pure tones when emitted in close vicinity (less than 2 m from the maternal abdomen) show that there are variations in the in utero SPL in both the human [48,49] and the ewe [41,50–52]. Some are systematic and related to the distance between the source and the transducer when the location of the transducer is changed in utero. Richards et al. [53] and Lecanuet et al. [52] found that the intrauterine noise level in pregnant ewes decreased as the distance from the sound source increased, although Nyman et al. [48] were unable to confirm this relationship in human subjects; Peters et al. [54] recently drew iso-pressure lines inside the uterus of a dead ewe filled with fluid and demonstrated that the attenuation of frequencies over 1000 Hz increased from the outside to the center of the cavity suggesting a 'wrapping around' effect. Others sources of variation are less clearly defined.

Major results — most of these obtained in sheep — can be summarized as follows:

1. The pressure levels of sounds at long wavelengths and low frequencies (< 300 Hz), were generally comparable in and ex utero: in utero measurements showed some variability with several dB SPL attenuation or enhancement (at 50 and 63 Hz in the sheep for Peters et al. [55]) depending on the research teams. When the wavelength of the frequency is longer than the diameter of an object reached by this frequency the entire volume of the object may be set in motion by this frequency without sound absorption.

2. According to Peters et al. [55], in utero pressure loss in the ewe was moderate between 400 and 1000 Hz and grew by 6.5 dB/octave on average between 1000 and 8000 Hz, thus peaking at 20 dB. Lecanuet et al. [52] found that this pressure loss started around 300–500 Hz depending on the distance between the hydrophone and the abdominal skin of the ewe. In the human, Querleu et al. [40] reported a similar pressure drop of 20 dB developed at a rate of 6 dB/octave, while Richards et al. [49] recorded a maximum attenuation of 10 dB at 4000 Hz. In all recent studies and in both species, maximum attenuation never exceeded 30–35 dB SPL up to 10 kHz.

3. A shift tendency has been found in the ewe at higher frequencies, the in utero pressure increasing and becoming even higher than ex utero pressure, a phenom-
already seen in the measurements of Vince et al. [50]. Peters et al. [55] observed this reversal from 12 500 Hz onwards and because they used 1/3 octave band noise stimuli, they found it to be linear. Using sweeping pure tones, Lecanuet et al. [52] have found such increases as low as 4000 Hz, the frequency values depending again on the depth of the hydrophone in the sheep. These increases appeared as a series of pressure peaks of resonance and anti-resonance probably due to standing waves caused by reflection of the short waves on the internal walls of the uterus.

**Differentiation of speech from background noise.** Data on voice differentiation and attenuation in utero agree with the results presented above. Recent acoustical recordings revealed that the maternal voice as well as external speech located near the mother clearly emerged from the uterine background noise components over 100 Hz. Recordings performed by Busnel [37] and Querleu et al. [40] (with an SPL level of 60 dB) have shown that both the mother’s and others’ speech: (a) was muffled and significantly attenuated in the high frequency components, (b) had well preserved prosodic characteristics, and (c) was somewhat intelligible since some phonemes (up to 30% in Querleu et al. [40]) and words could be recognized by adults when the recordings were performed far from the placenta. This is also true of external voices recorded from the pregnant ewe by Vince et al. [40].

**Human studies of in utero speech transmission.** In a recent work, Griffiths et al. [56] found that phonemes emitted by a male voice and recorded in a pregnant ewe had a mean intelligibility score of 55% (61% at 85 dB, 47% at 75 dB and 41% at 65 dB) while they had only a 34% mean score when emitted by a female voice. Compared to external recordings the intelligibility scores were respectively reduced by 29% and 50%. Analysis of VCV stimuli transmission showed that voicing information was better transmitted in utero than place or manner information, that was less preserved for a female than for a male speaker. In utero speech, in certain recording conditions, may even be clearly intelligible in the human [43,57] or the ewe (Lecanuet et al. [52]) at 90 dB SPL.

Human studies of in utero speech transmission performed with a hydrophone near the fetal head during delivery have all shown that there is a significantly better transmission of the maternal voice than of the external voice. Querleu et al. [40] and Benzaquen et al. [43] measured an overall 20 dB SPL attenuation of external voices, with no significant difference between male and female voices. In contrast, there is only an 8 dB SPL attenuation of the maternal voice. Richards et al. [49] recorded the maternal voice — which had an external 72 dB SPL level — 5 dB SPL louder in utero than ex utero. External voices — emitted at 90 dB SPL — suffered almost no attenuation at all: 2 dB for male voices and 3 dB for female voices; this represents a mean difference of only 8 dB between the maternal voice and external ones in this experiment, therefore comparable to the 12 dB difference reported in Querleu’s study [40]. It is of interest to note that results related to in utero maternal bleats in the pregnant ewe are similar. Gerhardt [41] recorded no attenuation in components up to 300 Hz, while Vince et al. [51] noted several dB SPL enhancement of these frequencies inside the uterus compared to simultaneous ex-utero recordings; pressure loss started only at around 1700 Hz.

**Sound isolation of the fetus.** Transmission of external pressures to the fetal ear is controlled by two factors that compose the isolation from the sound environment: (i) the attenuation due to the transmission to the amniotic cavity and (ii) the transformation of the in utero pressures into cochlear displacements. While, as demonstrated above, the first factor has been quite extensively described the proportion of the in utero pressures that reaches the fetal internal ear remains unknown. This proportion depends on the transduction mode at fetal head level; it is either directly made through the external and middle ear fluids or via bone conduction in the fetal head. For the moment, the pathways taken by acoustic pressures have not been defined.

Gerhardt et al. [59] attempted to define the isolation of the fetal sheep cochlea — i.e. the attenuation plus the biological transduction — by comparing the external pressure levels necessary to elicit identical cochlear potentials before and after delivery. Values of this isolation grew from 11 dB at 123 Hz to 45 dB at 2000 Hz. Abrams et al. [60] concluded that the fetal ear is not protected from low (<123 Hz) frequency signals, an important finding in view of the fact that low frequency signals are coded in the fetus by cochlear cells that will later code high frequencies and thus need to be protected in the prevention of future auditory deficits. Rubel and Ryals [61] showed that the cochlear tonotopy (i.e. the spatial distribution of frequency sensitivity in the cochlea) changes during maturation.

**2.3.2. Structural development of sensory transducers**

In the inner ear, the cochlea develops from the otocyst, a structure appearing around the 28th gestational day. It starts to curl by the 6th week, reaches its
full morphological development — measuring 3 mm and curled into 2 and 1/2 turns — by the 10th week, and its final adult size by the 20th week. The organ of Corti, which bears the auditory receptors, develops within the cochlea from the 8th week onwards. The first auditory cells (inner hair cells) and the three rows of outer hair cells can be seen as differentiated types of cells by the 11th week. None of them are functional at this age, nor at the 14th week when the cell positioning on the basilar membrane has reached its final stage [62].

According to Pujol and Uziel [63], who base their inference on the parallelism in chronology of cochlear development in humans and in every studied mammal, the human cochlea seems functional by the 18–20th week, while histological studies have shown that the auditory receptors are not completely mature at this time. The first cochlear potentials can be recorded in all animal studies at the same developmental stage. It is by the 20th week that the efferent innervation of the outer hair cells takes place, mature synapses being found between the 24th and 28th week [64]. Maturation of inner ear probably ends during the 8th month with the organization of afferent and efferent synaptic connections.

At the onset of cochlear functioning, auditory competencies, which have been characterized in animal studies, are poor. Electrophysiological responses can only be recorded for medium frequencies (1000–2000 Hz, depending on the species). Auditory thresholds are high (around 100 dB); there is no frequency discrimination and no temporal coding. However, these abilities improve rapidly, and gradually auditory thresholds decrease, temporal coding begins, frequency sensitivity widens first in the low frequency range, followed by the high ones, and finally unit frequency sharpens. The first cochlear potentials are evoked by mid-frequencies, although the base of cochlea, which usually codes high frequencies when mature, is the first cochlear zone to develop [61].

It has been thought that residual embryonic mesenchyma and amniotic fluid, still present in the external and middle ear at birth, may impair in utero middle ear functioning. However, the anatomical studies of MacLellan et al. [65] and the tympanometric studies of Keith [66] showed that they do not induce ear drum and ossicles stiffness. Nevertheless, it can be assumed that the middle ear is not necessary for fetal audition since it is adapted to the amplification of acoustic stimuli in aerial life. Without this amplification, clinical studies show that there is an average loss of 30 dB from the aerial environment of the outer ear to the liquid environment of the cochlea. In utero, since, the outer and middle ear are filled with amniotic fluid, and since liquids, tissues and bones have close conducting properties, the acoustic energy inside the uterine cavity can reach the cochlear receptors with negligible energy loss, thus, suppressing the need for an amplifying system. Middle ear transmission might still be possible, however, as pointed out by Rubel [67], its prenatal functioning is necessarily different from its postnatal one.

### 2.3.3. Evidence of fetal sensory functioning

Data obtained in several mammalian species have brought electrophysiological and neurochemical demonstrations of prenatal auditory function. In the human, cardiac and motor responses to several vibro-acoustic and acoustic stimulation have been studied and some evoked potential measurements have been performed during labor.

**Auditory evoked potentials.** Fetal brainstem and cortical auditory evoked potentials have been extensively studied in utero in the chronically implanted guinea-pig [68] and sheep [69]. These potentials display the same characteristics and the same developmental course as those recorded ex-utero. In the human, they have been recorded with electrodes placed on the fetus’ scalp during labor [70–72].

In the premature baby, short, middle and late latency evoked auditory responses have also been extensively examined. All three may be recorded, but are not consistently detectable at 24–25 weeks gestational age (GA). Detectability of major components progressively increases with age, and is stable by 30–32 weeks [73–75]. Brainstem responses are consistent and reproducible, but as previously inferred from animal studies (see above) — with very high thresholds (100 dB SPL) at 25 weeks. Thresholds gradually decrease with development and by 35 weeks GA are no more than 10–20 dB Hearing Level different from the threshold of adults. The five principal components showing neural activation from the cochlear nerve to the inferior colliculus are then regularly obtained but are still immature with regard to peak and inter-peak latencies and amplitudes.

**Neuro-chemical responses.** Local cerebral (14-C) 2-deoxyglucose uptake (2-DG). This method, which allows investigating fetal brain activity in utero through cerebral glucose utilization (energy metabolism), has been used in two animal models, the fetal guinea-pig [76,77] and the fetal sheep [78]. Pure tones, in guinea-pigs, and vibro-acoustic stimulation, in sheep, induce a marked increase in 2-DG uptake in auditory structures: in the brainstem in the guinea-pig, and in all auditory structures, including the auditory cortex, in the fetal sheep. In the guinea-pig, frequency-specific auditory labeling has been obtained to loud, external free-field pure tones up to 20 kHz. The location of the labeling in the cochlear nucleus and in the inferior colliculus is a function of the frequency of the tones. The tonotopic organization of the structures has thus been seen in utero.

**Behavioral studies.** When obstetricians began investigations into fetal responsiveness, guided by the observations made by many pregnant women that their
babies moved when a very loud noise occurred, they analyzed fetal responses to 'naturalistic' stimuli like warning horns [79,80] and wood claps [81-83].

**Administration mode and structure of stimulation:**

In the 1950s, experimenters started utilizing carefully defined acoustic stimulation, like pure tones and band noises, emitted through loudspeakers located at various distances from the maternal abdomen. Later, this **airborne mode** of stimulation was abandoned in favor of stimulation applied directly on the mother, near the fetal head, so as to avoid or minimize sound pressure loss. Two procedures were used:

(a) Stimulation was directly transmitted to the maternal abdomen by an oscillatory source (**vibro-acoustic mode**) usually a bone vibrator, a tuning fork, an electric toothbrush or the Electro-Acoustic Larynx (EAL). The EALs that were adopted in the 1970s, deliver broadband noises at a fundamental frequency of 87 Hz with multiple harmonics up to 20 000 Hz [84,85]. The surface of the instrument also vibrated at all frequencies between 10 Hz and 15 000 Hz. Intrauterine pressure estimation during EAL application has varied between 95 dB [86] to 138 dB [87]. Gagnon et al. [44] measured an average pressure during active labor of 95 dB SPL which can be as high as 123 dB.

(b) Stimulation was **air-coupled**, and in most cases the loudspeaker (usually part of headphones) was isolated from the mother's abdomen with a rubber or foam ring.

Vibro-acoustic devices are designed to propagate sound pressure more efficiently through tissues and fluids than through air. Impedance mismatches are therefore avoided. However, such devices may activate fetal cutaneous receptors which mature very early in development [7] and also possibly the saccus. The latter, which is part of the vestibular system, matures 2 weeks earlier than the auditory apparatus [88] and is known to be activated by loud low frequencies in different species including the human [89,90].

The air-coupled procedure is likely to result in important alteration of stimulus if the loudspeaker is applied directly to the mother's abdomen. The loudspeaker membrane is partially blocked thus producing frequency distortions and high frequency amplification. In contrast, when the loudspeaker is coupled with a rubber or a foam ring, it is the low frequencies that are more likely to be amplified. Therefore, the conditions produced by these two procedures are very different from the conditions of fetal auditory activation by external everyday sounds. This is probably why, in the 1980s, investigators came back to the use of airborne stimulation by placing loudspeakers at various distances from the maternal abdomen (1 m-10 cm) [45,47,91-96].

Since fetal studies began, various types of stimuli have been emitted via the different administration modes — airborne, air-coupled or vibratory: pure tones, various bandwidth frequency noises, high-pass filtered or unfiltered pink or white noises, and the EAL stimulation.

Even though the Sound Pressure Levels — measured at different ex or in utero sites — varied across a wide range of SPLs (from 65 to 123 dB SPL), most studies were performed at or above 100 dB SPL.

**Nature of fetal responses:**

It has been repeatedly mentioned before that the trivial signal of fetal audition perceived by any third trimester pregnant woman, was a fetal startle. Thus, the first systematic observations were concerned with the recording of **motor responses** and the concomitant heart rate changes.

1. **Motor responses:** Since the earliest observations, motor responses were classified either as isolated, strong, and sudden: i.e. startle responses, or as a sustained increase in fetal activity. Inhibition of ongoing movements [36,80,97,98] and habituation to the stimulus (cessation or a decrement of responses after repetition of stimulation) were also described very early [99], and regularly observed in many subsequent studies [38,100-102].

In order to detect fetal startles, Peiper and other early investigators had to rely either on visual or tactile estimation of fetal movement or on mother's perception of movement. More recent studies have demonstrated — as mentioned below — that mother's perception of movement is only partially reliable [103]. Researchers attempted objective recordings of maternal abdominal wall, independently of those evoked by mother's breathing. Different systems using pressure transducers [82,99,104] or piezo-electric accelerometers [105] were built to record the abdominal changes more precisely.

Analysis of fetal motor responses entered a golden age with the development of real time ultrasound scanning systems in the 1960s. A great number of studies produced startle response estimations by looking at a transverse view of the fetal trunk and lower limbs. This was either (i) performed on-line by the ultrasonographer who knew — and this might bias the observation — whether the fetus received a 'true' or a sham stimulation; and/or by a second observer who looked at the ultrasound image on a video screen placed in an adjacent room to the test room, or (ii) defined a posteriori by several independent observers on 'blind' videotapes of trials.

Latency of a specific movement has not often been computed. Experimenters usually looked for the occurrence of any movement before a previously fixed delay. Of course mean or median latency depends on this delay. When, this delay lasted several minutes, as in the case of the non-stress test, latencies for global movements ranging from 6 to 92 s were recorded [106] (average latency was 64 s when fetuses were in a quiet sleep state and 24 s in an active sleep state). With a few seconds delay, recorded latencies ranged between 1-2 s [47,86,107], or were less than 5 s [93,108]. Hepper and
Shahidullah [109] found an average latency of 0.34 s (evoked by a pure tone 250-Hz stimulation given between 80 and 100 dB) a value close to those recorded in the newborn studies. Comparison between maternal perception of response movements and ultrasonographically detected response movements showed that between 23 and 29 weeks, the mothers ‘feel’ approximately 50% of these movements (the rate of movements increase from 22% to 94% during this period) [103]. Over this age, mothers detect 95% of the movements induced by over 103 dB stimuli according to Yao et al. [110].

Local components of the startle response have also been ultrasonographically analyzed: head rotations and/or retroflexions, extension/extension and/or abductions of upper and lower limbs, hand or mouth opening [108,111]. Tongue protrusions, cheek movements and hand-to-face movements, the simultaneously spontaneous occurrence of which is rare, have been reported by Kuhlman et al. [107]. It should be noted that in the very first study performed using a vibroacoustic stimulus, Birnholz and Benacerraf [249] observed the eye-blink response, a motor activity which is less than easy to detect on the ultrasound imaging. This response, the most sensitive component of the startle response has an average latency of 0.031 s, [112] from 33 weeks to normal term in the premature baby. It occurs in utero in conjunction with cheek and forehead contraction with an average latency of 0.5 s. Using an electronic analysis procedure of ultrasonographic B and M imaging modes, Ishige et al. [113] computed eye-blink and eyeball rotation latencies. From 29 weeks on, their average latency was 0.099 s.

Looking at leg movements evoked during a 5-s airborne 105–110 dB broad band noise, Granier-Deferre et al. [92] and Lecanuet et al. [95,96] defined three types of fast movements: (i) a leg flexion or extension, followed or not by a return to the initial location, (ii) a double flexion at hip and knee levels (i) and (ii) were usually followed by a leg or body translation and rotation) and (iii) leg movements induced by a global body displacement. Median latencies ranged from 0.73 to 2 s depending on the acoustical structure of the noise. These values are far longer than the acoustic startle latencies recorded in the newborn: from 0.16 to 0.67 s [79,114–117]. However, it is difficult to assess this parameter, precisely because the leg was sometimes startling out of the frame, and these leg movements on average lasted 1.25 s (range, 0.34–3.1 s) whatever the fetal state.

Some very intense acoustical stimuli (>110 dB) and most vibroacoustic stimuli induce a long lasting (up to 30 min according to Gelman et al. [118]) increase in the number of movements compared to the pre-stimulation period. This increase usually reflects a change in fetal state, a point that is developed later.

2. Heart rate responses: Mostly phasic Heart Rate (HR) accelerations, but also sustained HR modifications, such as tachycardia, or a change in HR variability, were described as cardiac responses. Some authors studied both motor and cardiac responses and showed that motor response rates were lower than cardiac acceleration rates [36].

— Nature of response as a function of SPL:

Most studies on fetal audition have used loud stimuli. Two factors influenced the design of these studies. First, due to the idea that the fetus was sensorially isolated and to observations of pregnant women that their babies moved when a very loud noise occurred, it was believed that last trimester fetuses probably perceived only sudden, very loud, sounds. Second, the major clinical concerns, which were antenatal detection of deafness and diagnosis of fetal well being, required the use of acoustic stimuli that were easy to deliver and were known to elicit startle responses (sudden, strong motor responses), easily recognizable in daily medical practice. Thus, we will first review major results from the startling stimulation studies and then describe the promising data obtained with less intense, non-startling stimuli.

Startling stimulation:

1. Ontogeny of responses:

(a) Using pure tones stimulation, motor responses were first detected in vibro-acoustic and air-coupled studies at 27–28 weeks [97,119] or at around 7 months [36,118].

Cardiac accelerative changes were described as early as 5–6 months [102], 26 weeks [120], 27 weeks [97], 28 weeks [119], or 30 weeks [36]. Because of the important experimental design differences, no precise conclusion can be drawn concerning the ontogeny of fetal responses to pure tones. However, a gradual increase in responsiveness was observed with gestational age for both motor responses [36,97,121] and cardiac accelerative changes [36,80,97,120,121]. According to Sontag and Wallace [104], cardiac accelerations displayed larger amplitudes as fetuses get older. By 8 months, motor response and accelerative change rates found in most studies were between 70–90% [36,80,97,120,121]. These discrepancies may be explained by differences in response detection procedures and also because of stimulus characteristics. However, no systematic studies have been performed to analyze the effect of frequency, intensity or duration of stimulation on the proportion and characteristics of early fetal responses to pure tones.

(b) Vibro-acoustic studies using broad band noises and EAIs have shown that motor responses, i.e. reliable stimulus driven movements, were evoked in some fetuses as early as 24 weeks GA [86,123,124] and in all subjects at 26 weeks [125], 28 weeks [47,86,107,126] or 30 weeks GA [108,123,124,127]. According to Leader et al. [123] only 7% of fetuses responded by 23–24 weeks while there were 89% by 27–28 weeks. The onset of the response occurred earlier in females than in males: 75% of the 12 females responded by 25–26 weeks, compared to only 33% of the 15 males. All females responded by the
28th week, whereas 80% of the males responded at this age level. The authors consider this is according to established neurophysiological data as female infants mature earlier than males [128].

Very early diffuse motor responses of slow latency were recorded as early as 20 weeks GA by Shahidullah and Hepper [129] using a 110-dB broad band noise in an air-coupled situation. However by 25 weeks, the response had become an immediate startle-type one. According to the authors, the development of the outer hair cells, or some other maturational process occurring within the auditory system, may contribute to this change in responsiveness.

— Two classes of HR responses

Concerning cardiac responses, we have seen that administration of a 5-s EAL stimulation induces first an acceleration followed by a delayed response which consists of an increase in the number of HR accelerations between 10 and 20 min. Concerning the maturation of the first response, developmental time course compared to motor responses was delayed by 2–3 weeks [122,127,130] similarly to pure tone responses. Kisilevsky et al. [125] did not find reliable cardiac accelerations before 29 weeks. The pattern of this first type of response was found to be rather discontinuous 'with a rather abrupt change from no response to a relatively mature response between 29 and 31 weeks'. The authors mention that at 26–28 weeks, 9/12 subjects showed an average HR deceleration of 2.6 beats/min instead of the expected HR acceleration. Several maturational explanations are considered and it is noted that this result suggests an independent control of HR and movement response (the somato-cardiac effect of the concomitant movement should evoke an HR acceleration). According to Gagnon et al. [130], the initial HR acceleration shows an increase in its amplitude between 28 and 30 weeks as well as the appearance of an inverse relationship between the prestimulus baseline and this amplitude. The authors consider that the rapidity of this response after stimulation (< 10 s) indicates that it is provoked by direct stimulation of the autonomic nervous system, which is functionally mature by 30 weeks and not a response mediated through catecholamine release by the adrenal medulla. The delayed cardiac response — an increase in the number and incidence of gross fetal body movements that could persist up to 1 h in some fetuses — is found only after 33 weeks GA. In approximately 15% of term fetuses there is a profound tachycardia lasting up to 90 min [111,130,131], which does not correspond to any typical FHR pattern observed under resting conditions. In addition, fetal movements and breathing patterns are also severely altered after 33 weeks. Term fetuses breathe less and more irregularly following stimulation. Petrikovsky et al. [132] observed that fetal swallowing rate increased from 17% to 42% after a VAS. The same stimulation induced sustained fetal panting (125 breaths/min one day 117 the next day) in a 30-week at-risk fetus [133]. As mentioned above, these modifications reflect a change in fetal state provoked by the stimulation. According to Visser et al. [111], a small number of fetuses of healthy pregnant women at term showed a switch from fetal state 1F (quiet sleep) to either 2F (active sleep) or 4F (active wakefulness) following stimulation with the EAL. Under normal conditions, the human fetus experiences spontaneous transitions from state 1F to state 2F, and then, to state 4F.

2. Effects of stimulus characteristics, fetal behavioral state and risk status:

In near-term fetuses (35–41 weeks GA) as in newborns, responses evoked with loud vibro-acoustic or airborne stimuli (over 105 dB SPL) are modulated by the characteristics of both the stimulus and the fetal state.

— Effects of stimulus characteristics

(1) Acoustical structure

The three groups of recent airborne studies mentioned above demonstrated that broadband noise given at the same SPL, 110 dB, elicited much higher rates of accelerative changes and motor responses than pure tones or narrow-band noises. This is in contrast to the air-coupled and direct vibratory conditions where high proportions of responses were obtained with pure tones. A probable explanation is that the SPLs reaching the amniotic fluid are much greater in the latter condition.

(2) Pressure level

As mentioned before, most studies were performed with loud stimuli (over 100 dB SPL) that induced — more or less reliably — an HR acceleration usually accompanied by a motor response. In the airborne mode of stimulation, Kisilevsky et al. [93] found that the threshold intensity for a reliable HR acceleration is somewhere between 100–105 dB. Lecanuet et al. [96] found that when controlling fetal state, relatively high percentages of HR accelerative responses were elicited with octave-band noises presented at 100 dB in a high variability HR state: 50% at 2000 Hz and 55% at 5000 Hz, with an average amplitude of 18 beats/min for the two frequencies.

Whatever the stimulation mode, when acoustic pressure level of the stimulus was enhanced, motor and cardiac response rates increased, as did acceleration amplitudes [93,110,134]. A 5-dB SPL difference was sufficient to modify fetal responsiveness [93]. This general increase was observed independently of fetal behavioral state. However, both cardiac and motor responsiveness were greater in high HR variability (active sleep) than in low HR variability (quiet sleep) [95,135].

(3) Frequency/pitch

Contradictory results have been obtained in studies using pure tones (in air-coupled and vibratory modes of stimulation), responses rates being higher for high fre-
frequency stimulation than for low frequency stimulation or vice-versa. With broadband noises, given in the airborne mode of stimulation, higher pitched sounds induced more responses than lower ones [96]. Low frequencies, such as a 500-Hz centered noise, induced very few motor responses. When motor reactions were induced, the mean amplitude of FHR accelerations was higher (22 beats/min; ranging from 6 to 48 beats/min) than when there were no concomitant fetal movements (12.5 beats/min) thus reflecting a somato-cardiac effect.

Effects of fetal behavioral state

Since the work by Nijhuis et al. [136], four behavioral states have been classically recognized in the near term fetus: active (2F) and quiet (1F) sleep, active (4F) and quiet (3F) wakefulness. In 2F state (active sleep), both cardiac and motor responsiveness to acoustical stimulation are greater, cardiac accelerations have higher amplitudes and are more often accompanied with a motor response than during 1F state (quiet sleep) [95,96,135]. Schmidt et al. [135] also found a greater reactivity in quiet (3F) and active (4F) wakefulness compared to sleep states. We have seen that when acoustic stimuli were above 110 dB SPL, or VAS were given, response ratios appeared to be no longer modulated by state; when administered in quiet sleep these stimulation induced an immediate change to active sleep (state 2F) or wakefulness with movement (state 4F) [85,93,111], thus suggesting some disturbing or even stressful effect.

Effect of risk status

Kisilevsky et al. [137] studying 32- to 34-week fetuses whose mothers were hospitalized threatened by preterm delivery, found that when stimulated with a moderately strong vibro-acoustic signal subjects showed a delay in the latency of the HR acceleration response and weaker magnitude of this response (average over 1-s intervals) than non-hospitalized agemates. Since the magnitude of the hospitalized group was similar to that found in a 29- to 31-week non-hospitalized group the authors suggest that hospitalized fetuses have a less mature response than non-hospitalized ones.

After the introduction of antepartum FHR testing, several investigators using a variety of acoustic stimuli [138–142] have suggested the use of FHR response to external acoustic stimulation as an indicator of fetal health and metabolic status. Clinical use of Fetal Acoustic Stimulation (FAS) started with the introduction of vibroacoustic stimulation with the EAL [143]. According to Gagnon [144], the sensitivity of FAS or VAS used antenatally to predict intrapartum fetal distress or low 5-min Apgar score has been less than 60% and their positive predictive value less than 20%. These observations suggested that VAS may have evoked reactivity in fetuses with early compromise and raised concerns about using VAS to discriminate between the healthy and unhealthy fetuses. In the only randomized controlled trial of VAS for antepartum monitoring [143], no difference in outcomes was observed between the use of the VAS and a control group, followed with standard antepartum FHR monitoring. Clarkson et al. [145] tested 2628 women with singleton high-risk pregnancies. Currently available data obtained from these two studies suggest that the risk of intrauterine fetal death in the presence of a FHR response to fetal vibroacoustic stimulation is probably not higher than following a spontaneously reactive nonstress test (1.6 per 1000).

Capitalizing on data obtained in healthy fetuses mentioned above, Gagnon [144] recommends that if clinicians wish to use antepartum VAS to assess fetal health and save testing time, criteria for reactivity such as one FHR acceleration of <10 beats/min for <15 s and/or an increase in FHR baseline of <10 beats/min for <2 min following a 3-s stimulus would be adequate criteria after 30 weeks gestation. Occasionally, more than one stimulus may be required [143,145,146]. If no FHR response is observed, the interpretation of the results should take into account other factors that could influence FHR response to VAS. Concerning intrapartum tests Gagnon [144] recalls that persistently abnormal FHR patterns in women in labor have a false positive rate of 50% to predict adverse outcome. Normal FHR responsiveness to VAS might be falsely reassuring. This false negative rate also indicates that VAS may occasionally be a stimulus too strong to differentiate the healthy fetus from the acidotic fetus.

Non-startling airborne stimulation:

Sounds between 85 and 100 dB SPL ex-utero, do not induce startle responses or cardiac accelerations, but evoke moderate heart rate deceleration, unaccompanied by movement. For example, Lecanuet et al. [96] found that a 500-Hz octave-band noise emitted at 100 dB elicited only cardiac deceleration and that the deceleration had the same amplitude in quiet and active sleep (−10 beats/min). This type of response had been anecdotally mentioned by many authors [36,101,147,148,149]. Some of the decelerative responses were described as part of biphasic cardiac responses. Pilot studies confirmed that these cardiac decelerative responses: (a) could be reliably elicited in quiet sleep (1F) fetuses by various types of continuous or rhythmic airborne stimuli, emitted within this 85–100 dB range ex utero, and that (b) they quickly habituated to a repeated stimulus (given every 3–4 s). This made it feasible to examine the possibility of discriminative auditory capacities in the 36- to 40-week GA fetus. An habituation/dishabituation procedure derived from the work of Clarkson and Berg [150] on speech discrimination in the awakened neonate was used.

In a first study [151], fetuses which were exposed every 3.5 s to a pair of syllables ([ba] and [bi] or [bi] and [ba]) uttered in French by a female speaker, and emitted at the same pressure level (95 dB) displayed a decelerative response. Reversing the order of the paired
This discrimination may have been performed on the basis of an intensity difference between the [ba] and the [bi], since the equalization of these syllables was done on the basis of the sound pressure level, not the hearing level.

In the next study [152], a conservative data analysis procedure which took into account each subject's pre-stimulus HR variability was developed. This procedure defined for each subject: (a) whether the stimulus presentation and the modification of its acoustic structure induced a HR change, (b) whether the direction of the HR change was accelerative or decelerative, and (c) what its amplitude was. Results obtained by this procedure demonstrated that near-term fetuses exposed to a short sentence 'Dick a du bon thé' uttered by a male voice (minimum fundamental frequency: Fo = 83 Hz) or a female voice (minimum Fo = 165 Hz) at the same hearing level (90–95 dB SPL) and at 3.5-s intervals, reacted with a high proportion of decelerative responses (77% to the male voice, 66% to the female voice) within the first 10 s of stimulation compared to a group of non-stimulated subjects. After return to a stable HR pattern, the initial voice (male or female) was either replaced by the other voice or continued (in a control condition). A majority (69%) of the experimental subjects, displayed a HR deceleration to the change, while 43% of the control subjects displayed a weak amplitude acceleration [152].

The presence of these significant novelty responses showed that near-term fetuses may perceive a difference between the voice characteristics of two speakers, at least when they are highly contrasted for Fo and timbre. These results cannot be generalized for all female and male voices or for all utterances. It should be emphasized that in this experiment FHR change occurred within the first seconds of exposure to the novel stimulus, thus suggesting that only a short speech sample is needed for the fetal auditory system to detect an acoustically relevant change in speaker. Since the most obvious acoustic cues for the discrimination are fundamental frequency and timbre, near-term fetuses in quiet sleep may perform pitch discrimination as was found during quiet sleep in the newborn by Alho et al. [154] on the analysis of the EEG.

1. Fetal responses to musical stimuli:

Although every pregnant woman has noticed that the baby she carries seems to react differentially according to the type of music emitted in the environment. Data described above suggest that other factors than the type of music, i.e. its loudness, its pitch, and to a large extent, the behavioral state of the baby, may control the reaction of the fetus. Thus, the differential average increase of HR variability measured on a group of 20 subjects exposed to the air-coupled presentation of two distinct sequences of classical music by Olds [155] may partly be due to such effects. A global increase of the number of HR accelerations and movements is expected in response to the presentation of any loud sequence of stimuli, a response observed by Olds to the emission of 5 min of singing or piano music. An air-coupled presentation by Woodward [156] of 15 s of a sample of Bach's organ prelude given at 100 dB induced a high percentage of HR acceleratory responses (93%) in a High Variability state, much more than in a Low Variability state. Almost all of these responses started within 5 s of presentation of the stimulation.

Finally, the potential indirect effects of music on the fetus must be considered: those induced by the maternal response to this music. This is a very difficult task since the psychobiological impact of music on an adult depends not only on the style of the music but also on the personal history of this subject. Zimmer et al. [157] gave a 25-min sequence of music to future mothers via headphones (classical or pop music) and found that the fetuses of these mothers showed more body movements and less respiratory movements than during a silent period. This effect was more significant with the mother's favorite music. Conversely, no modification of fetal HR was found by Olds [155] during a presentation of music to the mother through headphones.

2. Fetal responses to maternal speech:

It was mentioned above that, looking for stimuli inducing fetal HR deceleration, we noticed that maternal speech had this potential. Preliminary unpublished data suggested that this response was most frequently elicited in Low HR Variability state (1F) and when the mother spoke with a 70 dB Leq level. Recent work by Masakovsky and Fifer [158] demonstrated that near-term fetuses tested in 1F state, showed a HR decrease from baseline during the last 5 s of a 10-s episode of outloud maternal speech. Silent or mother whispering episodes did not evoke a significant HR change.

2.4. Visual system

2.4.1. Potential sources of stimulation

In utero visual stimulation appears to be very limited; however Liley [159] recalls that — in a dark room — the amniotic cavity may be candled with a torch light, especially in the case of a polyhydramnios. Measurements performed during rat and guinea-pig gestation have demonstrated that if only 2% of incoming light was transmitted in utero below 550 nm, this value increases with wavelength of the signal to reach 10% around 650 nm [160]. Thus, a limited portion of external light may reach the human fetal retina when eyelids are open (this behavior starts at 20 weeks) or through the eyelids.
2.4.2. Structural development of sensory transducers

The otic vesicles out of which the retina will stem appear by 30–32 days of gestation. Major retinal morphogenetic events occur between months 2 and 4 of gestation. Rods and future cones can be found by the end of the 3rd month, but the development of photoreceptor cells is not completed before birth. This process lasts a few more postnatal months in the macula.

2.4.3. Evidence of fetal sensory functioning

The presumed restricted amount of visual input in utero has not stimulated the study of responsiveness to this type of sensory stimulation. A few studies have been conducted which suggested that: (a) switching on a bright light bulb in front of the abdomen of a pregnant woman induced fetal heart rate accelerations [161]; (b) an increase of fetal motor activity may be obtained after a sustained exposure to the light (20 min) but not after a series of ‘on and off’ switches [162]. However, heart rate changes induced by a cold light introduced during an amniocentesis represent more convincing data [163]. The ontogeny of visual evoked potentials has been described in the fetal sheep [164]. Stimulation was delivered by a tiny light source secured close to the eye.

3. Consequences of prenatal sensory experience

Prolonged exposure — for several weeks and even months — of a maturing sensory system to a large variety of external and/or maternal stimulation may have several types of effects at either structural, functional or behavioral levels. Concerning the former levels, prenatal activation of sensory systems may contribute to the normal development of peripheral structures and central connectivity, as well as to uphold their anatomic and functional integrity during prenatal maturation. Indeed, if the anatomical macro-organization of neuronal networks is genetically designed (neural pathways), more or less plasticity is possible according to species and systems, especially regarding micro-organization of neural networks (development and stabilization of dendritic arborisation and synapogenesis). Incoming sensory stimulation may play a crucial role during this period.

On a more general level, fetal stimulation may also contribute to the building of perceptual abilities (sensitivity, discrimination) and enable the fetal subject to process differentially sensory cues that will be relevant during postnatal life (induction of preferences). Numerous animal experiments and a few human studies (see review in [164,165] and [19] or see below) demonstrate that fetal sensory activation may alter, through learning, spontaneous pre- and postnatal responses to auditory and chemosensory stimulation. They may contribute to the organization of the newborn’s preferences for particular stimulation that will be encountered in the postnatal environment.

Fetal acquisitions can be seen pre- and postnatally. They can be inferred from a selective responsiveness to the presentation of a fetal stimulation or from the demonstration of a clear preference for this stimulation when presented in a choice situation.

3.1. Chemosensory stimulation

Animal studies have shown that behavior previously described as innate was in fact influenced by prenatal learning. The newborn rat pups show olfactory preferences or rejections based on prenatal chemosensory learning [166,167]. Rat fetuses exposed to apple flavor, show, when weaned, a drinking preference for an apple-scented beverage than for one scented with maple syrup [168]. Such a preferential orientation may happen in natural settings, independently of any artificial odorisation in the womb. It has been shown that newborn rats display a preference for the smell of the amniotic fluid in which they grew [166]. Similar data have been collected in the newborn sheep and human. Human neonates presented with the odor of their amniotic fluid display attraction responses on postnatal day two [32]. This attraction towards the amniotic odor is also observed later, on the 4th postnatal day [169].

In the present state of knowledge it is difficult to assess the duration of fetal learning. Reliable data, restricted to animal studies, deal with learning processes (imprinting, aversive learning) to highly biologically relevant stimuli (food, specific vocalizations, maternal odor) the consequences of which persist without visible alteration for a long postnatal period. This is the case for certain maternal olfactory signals the durable attractiveness of which has been demonstrated without any post-natally reinforced re-learning. Firstly, young rabbits conditioned postnatally to respond positively to novel odors do not modify their innate preference for the smell of the maternal nipple pheromone [170]. Furthermore, human newborns, bottle-fed from birth (thus having no exposure to breast or maternal milk odor) show, 2 weeks after birth, a clear preference for the smell of a breast-feeding mother versus the smell of their own mother's breast [171]. One could legitimately assume that after birth the large number of novel stimulations, offering many learning opportunities in conjunction with disruptions of recognition situations of familiar prenatal stimuli, might induce a vast reorganization of prenatal learning and of their retrieval ability which are due to extinction, generalizations and transfers. The long-term retention of prenatal chemosensory experiences might be embedded in the anatomical organization, the olfactory bulb being directly connected to several paleocortical areas involved in memory and emotional processing of sensory inputs.
3.2. Auditory stimulation

3.2.1. Prenatal effects of sound exposure

Structural and functional effects. Animal studies performed on species in which the auditory function starts after birth (mouse, rat, gerbil, cat, guinea-pig) have shown that the afferent input is necessary to establish and maintain a correct functioning of the auditory system and to the partial sound integration in the brainstem. Bilateral auditory deprivation starting before or during the period of appearance of cochlear potentials, causes the same anatomical alterations, but to a lesser extent, than a bilateral destruction of the cochlea: (i) a reduction in the number and size of the neurons along the auditory relays of the brainstem acoustic pathway, (ii) higher electrophysiological auditory thresholds, and (iii) a reduction in the ability to discriminate complex rhythmic structures. Monaural deprivation causes neuronal and electrophysiological alterations affecting mostly ipsilateral structures, dealing with binaural interactions. Several experiments have shown that sound deprivation would mainly induce a delay in the development of auditory sensitivity: impairment can be reversible if the deprivation does not extend to a critical period (see reviews in [172-175]). Such deficits impair auditory spatial localization [176,177].

On the other hand, prolonged exposure to selectively enriched sound environments — which do not induce any acoustic trauma — stimulates local dendritic growth [178], and modifies the reactivity of central acoustic units [179,180] which seems to facilitate certain discriminative auditory tasks. Thus, we may assume that sounds reaching the fetal ear might contribute to the structural and functional shaping of the auditory pathway.

Behavioral effects.

Habitation.

1. Motor and cardiac responses in non-pathological fetuses.

Experiments reported above [151,153] have shown that repetition at a short interval (every 3-4 s) of a 92–95 dB acoustic stimulus led to the disappearance of a decelerative cardiac response that had been induced by the first presentation of this stimulus, thus indicating an habituation to this stimulus. Due to their interest in the fetal diagnosis of potential neural defects, a large number of studies have been — and are still — performed to analyze fetal habituation to loud stimuli. These studies indicated that the number of stimulus presentations required to obtain habituation depends on (a) the type of observed response (motor or cardiac), (b) the defined habituation criteria (i.e. the number of trials inducing no response, and the use or not of a dishabituation stimulus), (c) the characteristics of the stimulus (spectral organization and duration, inter-stimulus time interval), and (d) the fetal behavioral state.

With an airborne auditory stimulation, given at or lower than 110 dB SPL ex utero, local and/or global components of the startle response significantly decreased or disappeared after only 2–4 presentations [79,80,94,97,105]. As in the premature baby or the term newborn, the fetal cardiac response is slower to habituate than the motor response. Significant reduction or disappearance of this response is obtained after 2–7 presentations [94,95,149].

When applying vibro-acoustic stimulation, motor response rate decrement is much slower than with airborne auditory stimulation. It takes at least 6–40 presentations to occur depending on fetal age, fetal condition and habituation criteria [123,182] (10–50 trials); [107,183] (16–18 trials); [107,185,186]. Among the 15 subjects on their 36th week of gestation tested on two successive days in the Leader et al. [123] study, 14 required fewer stimuli for habituation on day two. Infants tested after intervals of 3–4 days showed no consistent habituation pattern. The authors concluded that this seems to indicate some evidence of fetal memory that lasts for 24 h and not for 72.

The authors did not notice any effect of fetal state.

Motor habituation becomes easier to establish as gestational age increases: with a 12 stimulation habituation criteria, 31-week fetuses needed on average 10.3 stimulations to habituate and 40-week fetuses only 6.2 [107]. According to Groome et al. [187] who replicated this study from 28 weeks onwards and coded the strength of motor responses, there was no change whatever with age of the subjects but the decrease of the strength with stimulation was faster after 32 weeks than before this age.

Concerning HR responses, Leader et al. [188] tested habituation to three 5-s EAL stimulations. Stimulation two and three were given only when the HR rate had returned to the baseline for 2 min. The HR response was defined as the HR level 1 min after stimulation. There was a significant decrease in the response between the first and second stimuli as well as between the second and third stimuli. The mean time for the fetal heart rate to return to its baseline after the first stimulus was 5.8 min (range, 0.5–15 min), after the second stimulus 4.49

Habituation criteria (i.e. the number of trials inducing no response, and the use or not of a dishabituation stimulus), (c) the characteristics of the stimulus (spectral organization and duration, inter-stimulus time interval), and (d) the fetal behavioral state.
mothers tested three times (the second time 30 min after the first, the third time 20 min after the second) and the habituation rate of a group of fetuses of non-smoker mothers had taken 30 mg of phenobarbitone every 8 h for 3 days. While the two groups did not differ on a habituation test given day one, before the barbiturate ingestion, only three fetuses out of nine in the drug group had a normal habituation pattern on a test given on day 4–5. When retested after stopping the sedatives, their habituation pattern had returned to normal.

Kuhlman et al. [107] found that drug addicted mother fetuses habituate slower than those of mothers who do not take drugs.

(2) Alteration in inspired maternal oxygen

Leader and Baille [196] analyzed the effect on fetal habituation to their vibro-acoustic stimulus of breathing by the mother of only 12% oxygen during the test. This is equivalent to living at 13 000 feet above sea level and reduces the maternal Pao₂ from 99 mmHg to 44 mmHg. The arterial saturation, however, only falls to 86%. Two counterbalanced experimental groups had the 12% oxygen breathing either on a first or on a second test given the next day. In both cases, only one fetus out of eight and 10 showed a normal habituation pattern under this maternal breathing situation, while all fetuses in the experimental group having the 12% oxygen on day two, and 7 out of 8 in the group having the limited oxygen on day 1 showed a normal habituation pattern.

3. Fetal pathology:

Of two cases of Down syndrome tested for habituation to a pure tone stimulus by Hepper and Shahidullah [109], one failed to habituate and the other took longer to habituate than control subjects. One of the two who failed to show any change in its motor response latency died shortly after birth, although there was no detectable difference between the two antenatally.

In the VAS study by Leader et al. [183] giving three stimulation and measuring HR change, at risk fetuses showed abnormal habituation pattern (<9 or >50 stimuli) compared to the one they showed 3–4 days before (10–50 stimuli). Other subjects, whose mother smoked 40 cigarettes a day required 6 hr before fetal habituation returned to normal pattern. Hepper and Shahidullah [109] showed that fetuses whose mothers smoke required a greater intensity of stimulus to evoke a response compared to those whose mothers did not smoke.

In addition, Leader [191] compared the evolution of the habituation rate of a group of fetuses of non-smoker mothers tested three times (the second time 30 min after the first, the third time 20 min after the second) and the
More recently Feijoo [197] claimed to have associated the musical theme of Peter and the Wolf by Prokofiev (given at 60 dB SPL) with a state of deep maternal relaxation (presented as an unconditional stimulus inducing fetal movements) several times a week during the 6th, 7th and 8th pregnancy months. When tested on the 37th week, trained fetuses responded immediately with movements to the presentation of the musical theme, while non-exposed fetuses moved only 6–10 min later. Backwards presentation of the sequence did not have any effect on trained subjects.

3.2.2. Postnatal effects of sound exposure

Prenatal auditory experience may result in general and/or specific learning, the effects of which are seen in various postnatal situations. Familiar stimuli or classes of stimuli may — more or less selectively — soothe the crying newborn or elicit orienting responses during quiet states. Stimuli may ease their avoidance properties after the baby has been exposed to them during the fetal life. More convincingly, familiar stimuli or classes of stimuli can be preferred to unfamiliar ones in choice test situations (e.g. the non-nutritive high amplitude sucking).

Soothing and orientation responses.

Maternal heart-beat and other endogenous sounds:

Salk [198,199] first found that newborn babies daily exposed to the sound of an adult heartbeat emitted at 72 beats/min — a sound presumed to be familiar from the earliest fetal period — were soothe by this sound, slept sooner and gained weight more rapidly than non-stimulated babies. Salk’s work was followed by a series of investigations on the effects of maternally-generated internal noises. Initially, these studies were restricted to an examination of the soothing effect of maternal cardiac noises on the neonate. Results have not been conclusive, some describing a soothing effect which others did not confirm [35,146,200–209]. This is probably due to differences in experimental design, such as the use of different types of stimuli, different observation timings (short-term or long-term).

Murooka [35] comparing various stimuli, including recordings of the intrauterine background noise (i.e. recorded close to the placenta and thus including loud maternal cardio-vascular components; cf. the discussion on the acoustic structure of internal sounds above) concluded that any noise having an acoustical structure similar to that noise — and not only this very stimulus — had a short-term pacifying effect. This effect has been confirmed by Kato et al. [203], and by Asada et al. [210] who recorded heart rate and respiration rate modification in crying babies. Yoshida et al. [211] report a similar effect on irritable babies, lasting at least for the first 7 postnatal days. Yoshida and Chiba [212] showed that the intra-uterine noise emitted at 75 dB lowered the fundamental frequency (Fo) of crying and elicited positive facial mimics. Using a non-nutritive sucking choice procedure, DeCasper and Sigafoos [213] demonstrated that the heart beat sound used by Murooka et al. [35] had a reinforcing value for 3-day-old babies.

Speech sounds and musical episodes:

It has been mentioned above that speech sounds, especially those emitted by the maternal voice, were not masked by the intrauterine background noise. The prolonged exposure of the human fetus to such stimuli may thus have postnatal effects. Natural or synthetic speech sounds seem particularly attractive to the newborn who shows transient decelerative responses to the onset of their presentation [214,215], an effect that may however be induced by many other auditory low-pitched, moderately intense, stimuli [216,217]. Many studies conducted during the last 25 years have suggested that newborns process speech stimuli in a specific way different from other auditory stimuli (see review in Aslin et al. [218]). This is usually seen as a consequence of an inherited human sensitivity to linguistic sounds [219] more than the effect of a prenatal exposure to speech sounds. However, these explanations are not mutually exclusive.

The particular attractiveness of the mother’s voice on <2-week-old neonates has been described by several authors [220–223]. The explanation accounting for this phenomenon could be postnatal association of this voice with positive reinforcers rather than prenatal learning. However, conflicting evidence is presented below.

Concerning musical sequence, Feijoo [197] in the delivery room, and Hepper [224] on 4- to 5-day-old babies, observed that infants were significantly soothed and attentive to musical sequences that their mothers listened daily during the last 3 months of pregnancy. Feijoo delivered the bassoon part of Prokofiev’s ‘Peter and the Wolf’; in Hepper’s study the target stimulation was the musical theme of the mothers’ favourite British TV sitcom ‘Neighbors’.

Long-term habituation to startling stimuli. Prenatal learning is suggested by two studies of long-term habituation. Human and guinea-pig neonates are significantly less disturbed by a startling sound if they have been repeatedly exposed to it prenatally. The longer the prenatal exposure of human neonates — living in the Osaka airport neighborhood — to airplane noises, the better they slept compared to babies whose mothers had lived in the area of the airport for shorter times during pregnancy [225,226]. In the same line, neonate guinea-pigs were less responsive (no significant heart-rate change) to the vocalization of a Bantam hen than control animals, who had not been exposed to this sound during gestation [227].

Evidence for auditory preferences.

For the maternal voice:

Concerning maternal voice, studies performed with 2- to 4-day-old neonates (using a selective Inter Bursts (of sucks) Interval (IBI) duration reinforcement procedure
of the non-nutritive sucking) demonstrated that the mother's voice was not only attractive to newborns as mentioned above, but was also preferred to another female's voice [228,229]. The possibility of a very fast postnatal acquisition was again argued. The authors then compared the preference between airborne versions of these voices to their 'intra-uterine', low-pass filtered versions. No particular preference was evidenced by Spence and DeCasper [230] (while the newborns did prefer an airborne version of another woman's voice, this was considered to be a demonstration of a prenatal contribution to the neonates' general preference for the mother's voice). Finally, Fifer and Moon [231] and Moon and Fifer [232], using a modified version of the 'intra-uterine' mother's voice (either mixed or not with maternal cardiovascular sounds), found that newborns preferred an 'intra-uterine' form of their mother's voice over an airborne version. In addition, DeCasper and Prescott [233] found that 2-day-old babies did not prefer their father's voice to another male's voice even after 4-10 h of postnatal contact with their father. This postnatal contact was thus insufficient to induce a preference to this voice. Together, these results suggest that the absence of a preference for the father's voice is probably due to lesser prenatal experience with the father's voice than with the mother's voice.

Prenatal familiarisation with the maternal voice may explain why Hepper et al. [234] found that newborns discriminate normally-intoned speech from mother-intoned speech (i.e. with exaggerated contours) only for the maternal voice. Subjects discriminated maternal voice from a strange female voice, however.

For a speech sequence:
DeCasper and Spence [235] showed (using the non-nutritive IBI contingent sucking procedure) that 2- to 3-day-old newborns preferred hearing a story their mother had read out loud during 6 weeks before birth than a story that they had never heard. Since no difference was found during testing if the story was read by the mother or another woman's voice, prenatal learning of some acoustic features of the story, probably prosodic, is suggested.

For musical sequences:
Using the non-nutritive sucking procedure, Panneton [236] showed that newborns whose mothers had been singing a melody — using the syllable 'la' instead of the words of the song — changed their pattern of sucking in order to turn on a recording of this melody more often than the recording of an unfamiliar melody; both melodies contained the same segmental information (i.e. the syllable 'la') and the same individual notes, but the temporal order, duration and relative number of the notes were different in each melody. Woodward [156] exposed fetuses from the 34th weeks GA onwards either to a sequence of classical music or to a sequence of jazz music. With a different sucking procedure (i.e. prenatal-ly presented music being contingent to a sucking pause (tan IBI) and novel music being contingent to the onset of a burst of sucks in one test condition and vice versa in another condition), she found that newborns lengthened the pauses (reinforced by the 'familiar' music) and had a smaller number of bursts in the second part of a 10-min test than in a silent pre-test period in the first condition type of test.

For a speech sequence sung by the mother:In an experiment performed by Satt [237] with the DeCasper's non-nutritive sucking test 3 days after birth, babies had to choose between two recorded lullabies, both recorded by their mother. During the end of their fetal life they had been repeatedly exposed to one of the lullabies for which they showed a preference.

For the maternal language:
In the following studies, the neonates had some postnatal experience with the maternal language before they were tested, either for a specific preference for this language or for their capacity to discriminate between the maternal and another language. Using a non-nutritive sucking choice procedure, with both Spanish- and English-speaking women. Moon et al. [238] demonstrated that 2-day-old newborns preferred their mother's language to the other one. Demonstration of a preference for the mother's language at such an early age favors an interpretation of the data of Mehler et al. [239,240] in terms of prenatal familiarisation. In these last studies, 4-day-old babies discriminated between two languages (French/Russian or English/Italian), one of which being the mother's language. Moreover, babies born from French speaking mothers showed a higher average sucking rate during the habituation phase when the speech emitted during this period was French than when it was Russian, both languages being spoken by the same bilingual woman. Such a response persisted when babies were exposed to low-pass (<400 Hz) filtered versions of the two languages which kept only prosodic cues of the spoken sentences. In addition, babies born from mothers speaking neither French nor Russian were unable to discriminate between those two languages as if the absence of any familiar prosodic cue rendered the perception of differences impossible. Thus, such data may reflect either prenatal familiarisation to a specific language, augmented by 3-4 days of postnatal exposure to this language, or fast learning processes occurring during this neonatal period.

4. Conclusion

Human fetuses are, to a certain extent, able to memorize certain sensory properties (e.g. within the auditory and chemosensory modalities) of their environment. How does this ability work, especially considering that the fetuses spend much of their time in sleep states? Despite the fact that they have only very short periods
of wakefulness and that their brain is not mature enough to integrate sensory experiences, several experiments suggest that this does not prevent pre- and perinatal learning. Experiments on the learning abilities of cerebrolesioned animals and human neonates demonstrate that remaining infra-cortical structures may support considerable elementary learning ability [241,242]. Similar evidence has been provided for anaesthetized adult animals [243]. Moreover, one may recall that memory for events does not develop only as a consequence of conscious suprathreshold perceptions, but also after various 'subconscious', infrathreshold stimulation. It has thus been demonstrated on human adults that an odor delivered below the detection threshold (not consciously perceptible) in systematic conjunction with a stressful situation, may elicit negative attitudes and responses during subsequent encounters [244].

Extending Maurer and Maurer hypotheses [245] concerning the human newborn we confront a very peculiar representation of fetal perception. According to these authors the newborn (and thus the near-term fetus) would be continuously opened to sensory experience — even during sleep episodes. Full consciousness, defined as resulting from the interaction between several brain levels, would gradually develop during brain maturation. Sensory perceptions may be first organized following 'amodal' processes, introducing babies in a synaesthetic world: they might 'taste' the voice of the mother, 'smell' the touch of her hand, 'listen' to odorous, etc. The polysensorial world of the adult may be simplified into a monosensory experience. Studies performed on newborn rats by Spear and Molina [246] bring some experimental support to this hypothesis.

A more classical point of view regarding consciousness considers, along with Kouchner and Tassin [247], that the poor development of modulatory cortical neurons and the very limited development of associative intra- and inter-hemispheric pathways, do not allow the conscious processing of sensory inputs. Consequently, stored memories or more carefully stated acquisitions performed during the very first years of life (including the fetal period) cannot be voluntarily retrieved since they had been stored according to a processing mode that is not directly compatible with the functioning of the aroused child or adult brain. This does not lead to consider that early learning experiences do not retain their potential control on awakened behaviors, but only that the information stored cannot be retrieved directly in conscious states.

The corpus of fetal sensory research presented above may have important clinical impact. Indeed, the above survey of the relative literature has demonstrated that the clinical concern has been central in this research. Almost all studies of fetal responses to vibro-acoustic stimulation have been conducted in quest of a fast, practical and reliable diagnostic tool for fetal hypoxia. More than 80 papers have been published and the practice of the EAL stimulation examination has developed especially in the USA. Gagnon's recommendations [144] about the use of VAS have been mentioned above.

Cyclic changes in behavioral state are the major restriction to the systematic reliability of analysis of responsiveness to sensory stimulation as a diagnosis tool. Firstly, responsiveness of non-pathological fetuses as a function of state is not well-defined. Secondly, its study shows that there is a considerable interindividual variability (Lecanuet et al., unpublished data). Selecting a more sensitive dependent variable than HR changes and startle response could renew current perspectives on the predictive value of sensory responsiveness. A promising line of research seems to be the global computerized analysis of the succession of behavioral states of the fetus. Alteration of duration and structure of spontaneous transitions between states has indeed been found to correlate with unfavorable outcomes [248].

Acknowledgement

The authors wish to thank C. Granier-Deferre and M.-C. Busnel for their contribution to previous elaboration of several parts of this manuscript and A.-Y. Jacquet for her very helpful support in the preparation of the reference list.

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