Fetal Auditory Processing: Implications for Language Development?

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Abstract

Fundamental auditory processing abilities such as attention to, discrimination, recognition, and learning of sounds are critical properties of early neurocognitive function, necessary for the acquisition of language, detection of possible opportunity, and identification of impending danger. Over the past 35 years, researchers have characterized auditory processing in human fetuses, occasionally at mid-gestation and reliably from the beginning of the third trimester of pregnancy. Study results demonstrate that fetal gestational age, state of arousal, maternal (e.g., diabetes, hypertension, preeclampsia) and fetal (e.g., growth restriction) high-risk conditions as well as sound frequency, intensity, complexity, and duration influence perception. The finding of differential responding to sounds in fetuses in populations of low- vs. high-risk pregnancies is particularly salient because it has the potential of serving as a marker of neuropathology with one of the most compelling examples the association of atypical response to the mother's voice in growth restricted fetuses and later expressive language deficits. Future research is essential to a better understanding of the underlying mechanisms responsible for disparities in auditory processing, identifying individual fetuses and newborns at greatest risk for subsequent language deficits, and generating and testing novel prenatal and neonatal interventions to prevent or ameliorate communication impairments.

Keywords

Human • Fetus • Audition • Perception • Sounds • Speech • Voice • Language • Heart rate • Body movements

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Introduction

References to human fetal auditory perception occurred anecdotally in the Bible (e.g., Luke 1:39–44) and sporadically in the early scientific literature (e.g., Preyer, 1885/1937; Pieper, 1925; Sontag & Wallace, 1936). However, systematic study has a relatively brief history, beginning in the 1960s–1980s (e.g., Murphy & Smyth, 1962) following the ready availability of ultrasound equipment with sophisticated image processing techniques (see reviews by Kisilevsky & Low, 1998; Lecanuet & Schaal, 1996). Initial work (e.g., Murphy & Smyth, 1962; Dwornicka, Jasienska, Smolarz, & Wawryk, 1964; Bench, 1968) concentrated on auditory abilities in order to learn more about congenital deafness and quickly broadened to examine well-being more generally (e.g., Read & Miller, 1977). This chapter focuses on fetal auditory perception, using selected research primarily from our own laboratory which employed behavioural measures. The chapter begins with a brief theoretical background and overview of the structural development of the auditory system. This is followed by a review of the literature characterizing fetal sensory sensitivity with respect to hearing per se and auditory processing of speech and language. Subsequently, the influence of the uterine environment on fetal response to sounds is explored, particularly the relationship between maternal-fetal heart rate and pregnancy conditions associated with placental insufficiency. It finishes with evidence of a possible link between differential fetal auditory processing in appropriately grown vs. small for gestational age fetuses and later language deficits. Discussion and suggestions for future research are woven throughout. Given the nature of a chapter, there are limitations to what can be covered and such is the case here. The literature review is not exhaustive nor is research from nonhuman species included in a substantive way even though such studies have contributed significantly to our understanding of genetics, fetal physiology, metabolism, and neural development.

Brief Theoretical Background

The developmental origins of health and disease (DOHaD) model attempts to explain the phenomenon by which one genotype can give rise to a range of different phenotypes in response to different environmental conditions during early development (Barker, 2004; Bateson et al., 2004; Gluckman & Hanson, 2004). This epigenetic model of brain plasticity emphasizes the short- and long-term influence of the maternal–fetoplacental relationship. It arose largely from retrospective epidemiological studies demonstrating an association between newborn body weight and the risk for later adult diseases (e.g., hypertension, Barker, Bull, Osmond, & Simmonds, 1990; cardiovascular disease, Barker et al., 1993; diabetes, Hales & Barker, 1992). Based on such work, Barker (1994, 1995, 1997; Barker & Thronburg, 2013; Godfrey & Barker, 1995) put forward the fetal origins of adult disease hypothesis. He posited that fetal growth and development was especially vulnerable to nutrient and oxygen supply during periods of rapid cell division (i.e., critical periods) and that undernutrition at such times permanently changed the fetal body structure, physiology, and metabolism leading to disease in adult life, a phenomenon known as ‘programming’. Different fetal effects resulted in different long-term effects on functional capacity, metabolic competence, and responses to the later environment because the timing of critical periods varied for different tissues with organs becoming sensitive to environmental disparities at different times during organogenesis. The concept of programming underlies the DOHaD model. Over time, the model has been expanded beyond nutrition by demonstrations of other influences during pregnancy on offspring outcome such as maternal stress, both physiological and psychological (e.g., Laplante, Brunet, Schmitz, Ciampi, & King, 2008; King & LePlante, 2015; see Chaps. 12–14), maternal alcohol ingestion (see Chaps. 16 and 17), iron deficiency (see Chap. 15), and exposure to selective serotonin reuptake inhibitors (see Chap. 18).

Recently, Van den Bergh (2011; also, see Chap. 14) purposed the addition of behavior to the model: developmental origins of behaviour, health, and disease (DOBHaD). She argued that integrating early brain and behavioural development in a more elaborate way than the existing DOHaD hypothesis, would allow for a better elucidation of innovative, preventative, and interventional strategies, especially with respect to behavioral problems and psychopathology. The mapping of brain and behavior (and genes and behavior) is complex (e.g., Pennington, Snyder, & Roberts, 2007) and well beyond the scope of this chapter. Simply put, observations of fetal behavior and behavioral change provide a noninvasive method of determining and assessing brain function (Hepper, 1995; Hofer, 1988, 1994). Analyses of fetal behaviours in healthy populations are assumed to reflect functional development of the fetal nervous system during the prenatal period with behaviours emerging and developing continuously over gestation and childhood (Hepper, 2015; Hepper & Shahidullah, 1994). Moreover, perceptual studies in other species have demonstrated that experience (enhanced, species typical, or deprived) can affect the development of sensory systems and behaviour (e.g., Gottlieb, 1971; see Chap. 1). Experimental work in humans is limited. However, spontaneous or sensory elicited behaviors have been shown to differ in fetuses who are neurologically compromised (Horimoto et al., 1993) and as a function of newborn outcome (e.g., Kisilevsky, Hains, & Low, 1999a, 1999b, 2001; see Chap. 16). As such, they have the potential to serve as early markers of neuropathology or pathophysiology. Using behavioural measures, fetal sensory sensitivity has been characterized in both low- and high-risk pregnancy populations, including those associated with placental insufficiency (i.e., undernutrition), demonstrating differential auditory processing between groups as well as an association with early infant language abilities.

Auditory System Development: Concise Overview

The human ear begins development early in the embryonic period (Rubel & Fritzch, 2002) with the neural basis of hearing beginning in the cochlear hair cells (Moore, 2002; Pujol, Lavigne-Rebillard, & Uziel, 1991). By 22 weeks gestational age (GA), the adult number of four rows of outer hair cells and a row of inner hair cells are present on the epithelial surface in the basal cochlea (Pujol et al., 1991) and the cochlea matures over mid-gestation in the absence of auditory input (Rubel & Fritzch, 2002). It should be noted however, that while auditory input may not be necessary, other conditions during pregnancy (e.g., placental insufficiency, Rees, Proske, & Harding, 1989; Rehn et al., 2002) may affect the developing system. Beyond the cochlea, there is a complexity of overlapping layers of cells in the neural pathways leading to the auditory cortex (Cant, 1998) with maturation occurring in a peripheral to central fashion. Myelination of axons occurs at 26–28 weeks GA followed by rapid, synchronous conduction in brainstem pathways at 29 weeks GA (Moore, 2002). At this time, reliable onset of hearing has been observed in healthy, human fetuses (e.g., Kisilevsky, Pang, & Hains, 2000; Shahidullah & Hepper, 1993). The timing also coincides with the onset of reliable otoacoustic emissions (Morlet, Collet, Salle, & Morgon, 1993; Morlet et al., 1995) and auditory brainstem responses in premature infants (Ponton, Moore, & Eggermont, 1996). The predominant mechanism for fetal hearing in a fluid environment is thought to be bone conduction through skull vibration and fluid conduction from the cranial cavity to the inner ear (Sohmer & Freeman, 2001; Sohmer, Perez, Sichel, Priner, & Freeman, 2001). With the onset of hearing, experience with environmental sounds is available for adjustment of the cortical circuits. Moreover, maturation of the auditory system continues with axonal conduction time reaching maturity by 40 weeks GA

(Ponton et al., 1996); path length increases (Moore, Ponton, Eggermont, Wu, & Huang, 1996) and synaptic delays mature into postnatal life (Ponton et al., 1996).

Where in the fetal brain auditory stimuli are being processed is not completely understood. Joseph (2000) argues that responses to short duration, relatively loud white noise are most likely reflexive (i.e., a startle), mediated by the brain stem. But what about longer duration, lower intensity sounds such as speech or music? Results from early imaging studies (Draganova et al., 2005; Hykin et al., 1999) reveal some cortical activity during the third trimester of pregnancy. However, mature axons are present only in the most superficial layer of the cortex and it is thought that it receives little auditory information (Moore, 2002). Another possible site is the inferior colliculus where temporal and spectral aspects of sound are both topographically, but mutually orthogonally, mapped (e.g., Eggermont, 2001). Firm conclusions await future research.

Fetal Auditory Processing: Background

From audio recordings from inside the uterus obtained following delivery, Querleu and Renard (1981), Querleu, Renard, and Crepin (1981), Querleu et al. (1986), Querleu, Renard, Versyp, Paris-Delrue, and Crepin (1988), Querleu, Renard, Boutteville, and Crepin (1989) demonstrated that environmental sounds were available to the fetus from both inside (e.g., maternal heartbeat, bowel sounds) and outside (e.g., voice, music) of the uterus. Individual speech sounds were muffled but the pitch curve of voices was retained absolutely (Querleu et al., 1986). Uterine attenuation was estimated to be about 35–40 dB (e.g., Abrams, Gerhardt, & Griffiths, 1993; Richards, Frentzen, Gerhardt, McCann, & Abrams, 1992) with greater attenuation of high vs. low frequencies (Walker, Grimwade, & Wood, 1971; Querleu et al., 1986).

The fetus is not directly accessible and auditory sensitivity typically has been studied using changes in heart rate and body movements in response to acoustic probes. As noted above, in healthy populations, such behaviors reflect normal central nervous system development (Hepper, 1995; Hepper & Shahidullah, 1994; Hofer, 1988) and provide a noninvasive method of determining and assessing prenatal brain function (e.g., Hofer, 1994; Kok, den Ouden, Verloove-Vanhorick, & Brand, 1998; Low et al., 1992). Fetuses are more responsive in active compared to quiet behavioral states (Schmidt, Boos, Gnirs, Auer, & Schulze, 1985). However, states [quiet (1*F*) and active (2*F*) sleep, quiet (3*F*) and active (4*F*) awake, see Chap. 6 for a detailed description] are not reliably identified electrophysiologically until about 36–38 weeks GA (Nijhuis, Prechtl, Martin, & Bots, 1982) and, even at this late gestation, may be indeterminate or atypical. Furthermore, in some high-risk pregnancy conditions (e.g., maternal diabetes, fetal growth restriction), states may be delayed or disturbed (see Chap. 5). Thus, in order to use the same procedure over gestation and with low- and high-risk pregnancies, as a control for state effects, responding on stimulus vs. sham/silent control trials or periods has been compared to determine stimulus driven behavior.

Fetal Auditory Processing: Hearing

The onset and functional maturation of reliable responding to airborne sound which indicate hearing in healthy, low-risk fetuses was described using a short duration (2.5 s), relatively loud (110 dB), high-pass filtered (800–20,000 Hz) white noise (Kisilevsky et al., 2000). From 29 weeks GA, fetuses responded with heart rate accelerations and body movements. With advancing gestation, the magnitude of the mean cardiac acceleration increased from about 9 to 12 beats per minute (bpm) and the threshold to elicit a response decreased from 110 to 105 dB SPL. At term, our laboratory as well as others have shown that increasing the sound complexity of the stimulus [e.g., pure tone to filtered white noise to

vibroacoustic[1] (mechanical touch + sound); Kisilevsky & Muir, 1991], the frequency (e.g., 500 Hz to 2000 Hz to 5000 Hz; Lecanuet, Granier-Deferre, Cohen, Le Houezec, & Busnel, 1986; Lecanuet, Granier-Deferre, & Busnel, 1988), or the intensity (e.g., 100 dB to 105 dB to 110 dB; Kisilevsky, Muir, & Low, 1989: Lecanuet et al., 1988) will increase the magnitude of the heart rate acceleration. The cardiac response to these brief duration, loud, repeating trains of rapid onset, high frequency sounds which have a response latency of about 4 s, peak at about 12–13 s, and return to baseline at about 20 s (e.g., Kisilevsky et al., 1989) is most likely part of a startle response (Joseph, 2000).

Fetal Auditory Processing: Speech and Language

In order to examine auditory processing with respect to the foundation for language development, more ecologically valid speech stimuli have been presented at longer durations (e.g., 30 s to 3 min) and lower stimulus intensities (e.g., 80–95 dB) so as not to elicit a startle. Collectively, the results of such studies have shown that fetuses discriminate segmented speech sounds and voices over the last trimester of pregnancy. At 36–40 week GA, they discriminated vowel sounds (/i/and /â/; Groome et al., 1999a), the reversal of pairs of consonant–vowel sounds (babi to biba, biba to babi; Lecanuet, Granier-Deferre, & Busnel, 1989) and a change in the gender of a speaker reading a sentence (male to female, female to male; Lecanuet, Granier-Deferre, Jacquet, Capponi, & Ledru, 1993). Younger fetuses, 26–34 weeks GA, also discriminated vowel sounds (/ee/ and /ah/), although higher intensity levels were required to elicit responding (Zimmer et al., 1993). Because these findings can be explained by the acoustic properties of the signal (Joseph, 2000), the influence of experience with such sounds is unclear.

Moreover, research demonstrating maternal voice discrimination (e.g., Kisilevsky et al., 2003) provides convincing evidence that responding is influenced by in utero experience with speech and language. Low-risk, healthy fetuses have been shown to discriminate between their mother's tape-recorded voice and her speaking directly. Without training, audio recordings vs. direct speaking elicited more fetal body movements (Hepper, Scott, & Shahidullah, 1993) and an increase in heart rate (Lee & Kisilevsky, 2014); with 6 weeks of training, fetal heart rate also increased to the audio recordings (Krueger, Cave, & Garvan, 2015). Differential responding in the absence of training might be attributed to a novelty response. Normally, every time that the mother speaks aloud (not whispering), the fetus is exposed to her voice through bone conduction and fluid vibration. Such repeated presentations can lead to habituation. In contrast, an audio recording represents the mother's voice coming from a different place (i.e., outside the uterus) and filtered by the maternal abdominal tissues. While many of the prosodic characteristics of her voice would be retained, intensity, direction, and speech sounds would vary. These resulting changes could represent novelty to the fetus, thereby capturing and renewing fetal attention.

The mother's audio-recorded voice appears to be a particularly salient stimulus for the fetus. In a meta-analysis of laboratory data, we (Kisilevsky & Hains, 2011) found that the onset of a cardiac response to her recorded voice vs. silent control occurred at about 32–34 weeks GA. The initial response was biphasic, a small heart rate decrease followed by an increase. Over gestation the response matured and, by term, the fetus showed only a heart rate increase. Also by term, we (Kisilevsky et al., 2003; Kisilevsky et al., 2009) have shown that fetuses respond differentially to their own mother's voice vs. a female stranger's (previous mother in the study) reading the same story. Across studies, the fetal response has been an increase in heart rate to their mother's voice vs. a

[1] The device used in our laboratory to deliver a vibroacoustic stimulus was an Allied Traders, hand-held, battery powered, cylindrical-shaped (3.5 cm × 25.2 cm) body massager. Frequencies ranged from about 0 to 8000 Hz; the average airborne sound intensity was 75 dB with an average peak of 86 dB A. A lower magnitude of fetal heart rate response and fewer trials to habituate were demonstrated using this vibrator vs. an artificial larynx, indicating a less intense stimulus (Kisilevsky, Fearon, & Muir, 1998).

small decrease, no response, or an offset response to a female stranger's voice. Clearly, to discriminate between the mother's and a female stranger's voice, the fetuses must have had experience with and learned some characteristic of her voice. Given exposure every time that the mother speaks, her voice most likely served as a ubiquitous environmental sound with learning occurring over repeated exposures. The effect is not a generalized effect of hearing a voice because the behavioral effects of hearing the mother speaking directly vs. her audio-recorded voice and the audio-recorded mother's vs. female stranger's voices are different.

These behavioral findings are in keeping with those using functional magnetic resonance imaging (Hykin et al., 1999; Jardri et al., 2012) which reported selective fetal cortical processing for the mother's vs. an unfamiliar voice at 34 weeks GA (Jardri et al., 2012) and fetal cortical activity at term in response to an audio recording of the mother reading a nursery rhyme (Hykin et al., 1999). Taken together these findings indicate attention, discrimination, and some level of cortical processing of the mother's externally presented voice.

It could be hypothesized that fetal recognition of the mother's voice is based on prosodic cues (i.e., the pitch and emphasis contours that give more meaning to speech) as has been suggested for infants (Floccia, Nazzi, & Bertoncini, 2000). However, preliminary analyses of unpublished data in our laboratory suggest an alternate explanation. Mixed model analysis of variance (ANOVA) used to compare heart rate response in 30, 35–37 week GA fetuses to a 2-min audio recording of the mother's voice played backward ($n=20$) vs. forward ($n=10$) showed a cubic effect over time [$F(1, 28)=4.559$, $p=0.04$, partial $\eta^2=0.140$] but no difference between voice direction. As can be seen in Fig. 8.1, the mother's voice played forward and backward elicited a similar pattern of response. Given that manipulation of the voice to its reverse changes the temporal characteristics (prosody), while retaining pitch, frequency, and tone, it would appear that some other characteristic of her voice, or perhaps prosody in combination with some other voice characteristic(s), is being learned during repeated exposure.

Our studies (Kisilevsky et al., 2009) which employed a familiar-novelty paradigm to compare fetal response to the native vs. a foreign language, the mother's vs. female stranger's voice, female stranger's vs. mother's voice, and mother's vs. father's voice (father defined as an adult male cohabiting with the mother during the pregnancy) provide support for the salience of the mother's voice and the conclusion that near-term fetuses have learned some characteristic of her voice as well as their native language. For example, following familiarization with the mother or a female stranger reading in their native language (English), fetuses showed a novelty response to a stranger speaking in a foreign language (Mandarin) but not their native language, replicating previous findings with newborn infants (e.g., Mehler, Bertoncini, Barriere, & Jassik-Gerschenfeld, 1978; Mehler et al., 1988). Following familiarization with either their own mother or a female stranger reading the same passage, fetuses showed a novelty response limited to their own mother's voice, indicating that they recognized the change in speaker from stranger to mother. A novelty response was not observed to a stranger's voice when the voice was changed from mother to stranger, although there was an offset response following termination of the stranger's voice, indicating that the fetuses had heard the voice. When the voice was changed from mother to father, again a novelty response was not observed but an offset response following termination suggested that the fetuses had heard his voice. Subsequently, when response to the mother's vs. father's voice was compared following a week of training with the father speaking to the fetus in his natural voice, a heart rate increase was elicited to both voices, although the magnitude of the heart rate increase to the father's voice appeared to be lower (Lee & Kisilevsky, 2014). Further, after birth, when these same fetuses were tested in a voice preference task, they preferred their mother's voice. Taken together, these findings indicate that repeated exposure prenatally to the maternal voice and the native language sets up some neurological modification that ultimately leads to memories of specific voices and language. Moreover, the structure

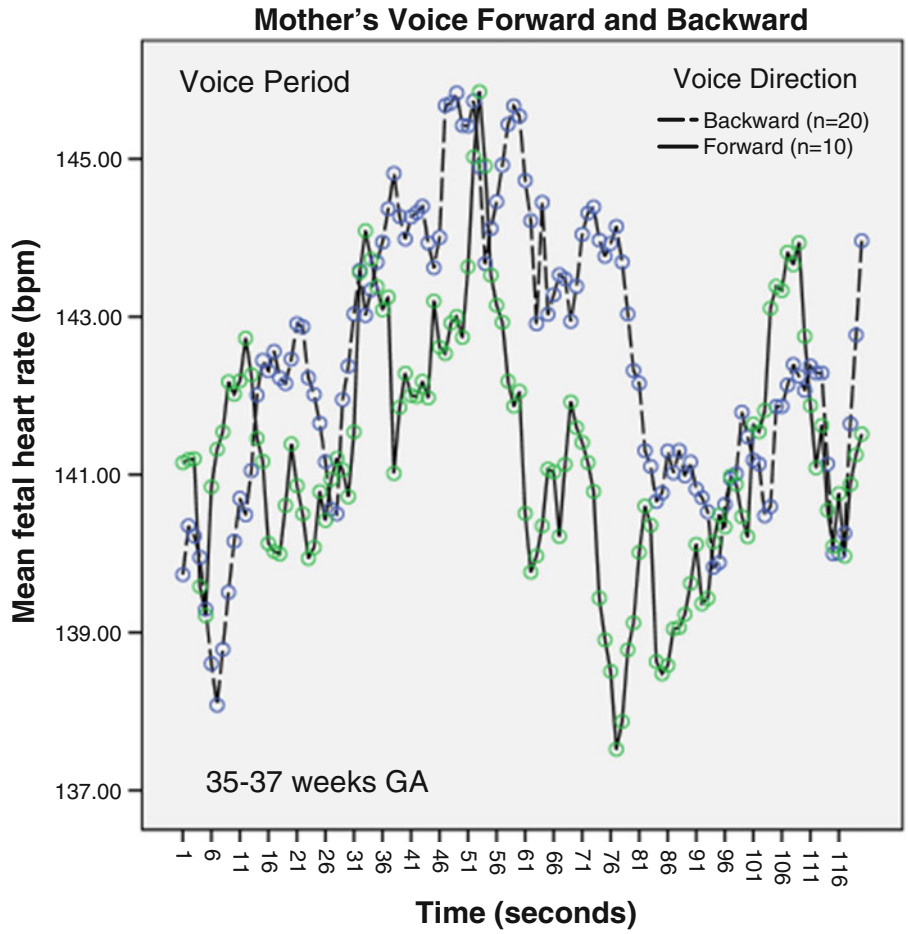

Fig. 8.1 Mean fetal heart rate over 120 s during the playing of the mother's voice forward or backward for fetuses at 35–37 weeks gestational age

and function of the fetal auditory system is not developing in isolation and could be influenced by simultaneously occurring changes in other fetal or maternal biological processes. Our laboratory has examined two possible influences: the relationship between maternal-fetal heart rate and auditory processing in high-risk pregnancies (e.g., threatening preterm delivery, conditions associated with placental insufficiency).

Influence of the Uterine Environment: Maternal–Fetal Heart Rate

While maternal–fetal biological linkages are well characterized and the implications of the symbiotic relationship for fetal development and survival are clear, the nature of the maternal–fetal cardiac relationship has not been as well elucidated. Such an understanding is important when characterizing fetal sensory sensitivity using changes in heart rate measures to ensure that any influence on the fetal response by the maternal system or maternal–fetal system interactions can be taken into account. A brief summary of selected studies is presented here. (For more in-depth coverage see Chaps. 7 and 23) Results of early studies occurring during maternal rest found no relationship between maternal and fetal heart rate measures (e.g., Lewis, Wilson, Ban, & Baumel, 1970) and no reliable periodicities during maternal sleep (e.g., Hoppenbrouwers et al., 1978). More positive results were reported as recording and analysis technologies advanced. In low-risk

pregnancies, a relationship between the maternal and fetal heart rate over 1 and 24 h (e.g., Patrick, Campbell, Carmichael, & Probert, 1982) as well as an association between the maternal parasympathetic indicator (PNS = high frequency/total power) and number of fetal heart rate accelerations (Swansburg, Brown, Hains, Smith, & Kisilevsky, 2005) was reported. Employing fetal cardiotocographic and maternal electrocardiographic measures, no synchrony was observed between maternal and fetal heart rate (DiPietro et al., 2006). Moreover, results of studies using magnetocardiography found occasional beat-to-beat coupling between the fetal and maternal cardiac systems (Van Leeuwen et al., 2003) which could be influenced by controlling maternal breathing rate (Van Leeuwen et al., 2009). Follow-up using surrogate computer modelling, led the researchers to conclude that the synchrony detected was more likely statistical rather than a physiological interaction (Riedl et al., 2009). Examining maternal heart rate variability measures [low frequency power (LF), high frequency power (HF), total power, parasympathetic nervous indicator (PNS = HF/total power), and sympathetic nervous system indicator (SNS = LF/HF)] in our laboratory (Brown, Lee, Hains, & Kisilevsky, 2008), no effects on fetal heart rate were found for any measure in a group of low-risk pairs in normotensive pregnancies. However, fetuses in a hypertensive group whose mothers had a higher PNS indicator were reported to have lower heart rates while the mother was at rest.

To explore associations between maternal and fetal heart rate during rest, data collected simultaneously using the same electrocardiographic equipment (Monica AN24, Monica Healthcare, Nottingham, UK) was extracted (Monica DK version 1.6) from our laboratory low-risk pregnancy database (unpublished) for the preliminary analyses reported below. For 33 pairs, correlational analyses of grouped data revealed no association ($r = 0.03$, $p = 0.85$) between the average maternal and fetal heart rates over 20 min of rest which is in contrast to the positive results reported for longer observation periods (Patrick et al., 1982). Nevertheless, when the pairs were examined individually, the results were mixed (see Table 8.1); significant small positive (18 %) and negative (45 %) correlations (range of r values −0.33 to 0.33) as well as no correlation (36 %) were observed among the pairs.

To explore the influence of changes in one heart rate on the other, fetal heart rate was delayed

Table 8.1 Correlations between average maternal and fetal heart rate in 2-s epochs over 20 continuous minutes while the mother was at rest for each pair separately

Association between maternal and fetal heart rate over 20 min during rest								
Positive correlation			Negative correlation			No correlation		
Pair #	*r*	*p*	Pair #	*r*	*p*	Pair #	*r*	*p*
01	0.13	0.01	04	−0.16	0.000	02	−0.07	0.08
17	0.26	0.000	07	−0.23	0.000	03	0.02	0.62
18	0.15	0.000	09	−0.33	0.000	05	0.06	0.18
38	0.09	0.02	22	−0.14	0.01	08	0.01	0.91
43	0.15	0.000	23	−0.19	0.000	11	−0.02	0.71
50	0.33	0.000	25	−0.11	0.01	26	0.02	0.72
			29	−0.22	0.000	27	−0.04	0.28
			30	−0.17	0.000	28	0.08	0.07
			37	−0.14	0.000	40	0.04	0.37
			39	−0.27	0.000	48	−0.01	0.80
			41	−0.10	0.02	52	0.01	0.77
			42	−0.21	0.000	53	0.04	0.34
			49	−0.27	0.000			
			54	−0.12	0.01			
			56	−0.20	0.000			

by 2 and 4 s with respect to the maternal heart rate and the reverse; none of the delays resulted in a meaningful change in any relationship. Subsequently, to further characterize the relationship, fetal and maternal heart rate variability measures were calculated for the second, 10 min of a 20 min recording while the mother was at rest for 40 pairs using custom software. Fetal heart rate variability measures (LF: 0.08–0.2; HF: 0.4–1.7) were based on David, Hirsch, Karin, Toledo, and Akselrod (2007) and maternal measures (LF: 0.04–0.15; HF: 0.15–0.5) on the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (1996). Preliminary analyses revealed significant maternal–fetal associations limited to HF power ($r=-0.37$, $p=0.02$) and PNS indicator ($r=-0.38$, $p=0.01$); both were negative. LF power ($r=0.21$, $p=0.19$), total power ($r=-0.19$, $p=0.25$), and SNS indicator ($r=-0.22$, $p=0.17$) showed no association. Using a median split of the maternal PNS indicator to create two fetal groups, fetal heart rate was examined over the 20 min of rest for the 33 pairs above for whom maternal–fetal heart rate correlations had been calculated. In keeping with our earlier report (Brown et al., 2008), no effect of maternal PNS was observed on spontaneous fetal heart rate change over time in this low-risk sample. Repeating the analyses using a median split of maternal HF, fetal HF and PNS, separately, also showed no effect for any of the heart rate variability measures on fetal heart rate during rest. Collectively, the results over studies using different technologies indicate that, during rest, the maternal–fetal heart rate relationship is complex and may be dependent on the specific heart rate parameter measured/analyzed, the length of observation time, the recording instruments, pregnancy risk status, and whether the data are from an individual pair or aggregated over group. None of the maternal or fetal heart rate variability measures had an effect on fetal heart rate in low-risk, uneventful pregnancies.

Studies of the association between maternal and fetal heart rate measures collected during sensory stimulation are rare. Recently, suppression of maternal heart rate within 5 s of an auditory elicited fetal startle response using a popcorn rattle was demonstrated (DiPietro et al., 2013). Mothers wore headphones with music and eye coverings to mask the sounds being delivered to the fetus. To explore this phenomenon, data were extracted for 20 maternal–fetal pairs for whom a 120-s audio recording of the mother's voice had been delivered to the fetus while the mother wore headphones through which masking music was played. Repeated measures analysis of the mothers' heart rate over 120, 20, 10, and 5 s in the period before vs. during the voice presentation, showed no period, time or interaction effects at either 5 or 20 s before vs. during the playing of the voice (Huynh–Feldt conservative probability reported for all repeated measures analyses). However, over the 10 s before vs. during the fetal stimulus, there was an effect of period [$F(1, 19)=4.786$, $p=0.04$, partial $\eta^2=0.201$] which was linear ($p=0.04$, partial $\eta^2=0.201$). Maternal heart rate decreased an average of 2 bpm over the first, 10 s following the onset of the voice recording.

Over the entire 120 s, there was a time effect [$F(119, 2261)=3.728$, $p=0.000$, partial $\eta^2=0.164$] which was qualified by a period by time interaction [$F(119, 2261)=2.095$, $p=0.02$, partial $\eta^2=0.099$] which was linear ($p=0.04$, partial $\eta^2=0.199$); over both periods, there was a gradual increase in the mothers' heart rate. These results provide a partial replication of the earlier findings. Taken together, the similar observation over laboratories using differing methodologies indicates an initial maternal heart rate decrease following the onset of a fetal auditory stimulus which elicits a fetal heart rate increase and/or motor response. The effect is not likely attributable to the stimulus per se because, in both laboratories, the sounds were masked to the mother. It could be that fetal movement during a popcorn rattle which would elicit a startle influenced the maternal heart rate change, although this is not likely for the maternal voice stimulus as it was below the threshold for a startle.

To further explore the issue, the relationship between maternal and fetal heart rates and heart rate variability parameters were examined using data from these same 20 pairs. As can be seen in Table 8.2, the percentage of pairs showing a

Table 8.2 Relationship between maternal and fetal heart rate before, during, and following presentation of a 120-s audio recording of the mother's voice to the fetus

Voice	Before		During		Following	
Pair #	*r*	*p*	*r*	*p*	*r*	*p*
01	0.11		0.20	0.02	0.09	
02	–0.27	0.01	–0.21	0.02	0.12	
06	0.18	0.04	–0.30	–0.01	0.05	
07	–0.17		–0.03		0.41	0.000
09	0.08		0.46	0.000	–0.10	
11	0.01		0.31	0.01	0.40	0.000
17	0.12		0.54	0.000	0.09	
18	0.08		–0.08		0.24	0.01
20	–0.10		–0.35	0.000	0.02	
22	–0.34	0.000	–0.04		0.65	0.000
23	0.03		–0.26	0.01	–0.17	
25	–0.30	0.01	–0.19	0.04	–0.11	
26	–0.27	0.01	–0.61	0.000	–0.21	0.02
27	–0.02		0.37	0.000	0.08	
28	0.09		0.23	0.01	0.08	
29	–0.12		–0.52	0.000	–0.09	
30	0.41	0.000	0.24	0.01	–0.10	
37	0.03		–0.21	0.02	–0.06	
38	0.10		–0.22	0.01	–0.13	
39	0.13		0.19	0.04	–0.10	

Note: Only significant *p* values are included

significant, small to moderate heart rate relationship during the playing of the mother's voice increased substantially from 30 % before to 85 % during the playing of the mother's voice and then dropped again to 25 % following the offset of her voice.

While this is a small sample and the findings are yet to be replicated, the dramatic increase in relationship between the maternal and fetal heart rates limited to the period of an auditory stimulus played to the fetus (mother was masked) suggests that changes in fetal heart rate or some other physiological process could influence the maternal heart rate. Alternatively, given that 63 % of maternal–fetal pairs showed a relationship (positive or negative) between heart rates over a 20-min period during rest, it could be that fetal stimulation simply demonstrated a relationship more efficiently over 2 vs. 20 min. Only 55 % of pairs common to both analyses illustrated in Tables 8.1 and 8.2 showed a maternal–fetal heart rate relationship both during rest and stimulation which does not provide strong support for the latter interpretation.

An effect of heart rate variability (i.e., HF) on fetal heart rate following the offset of auditory stimulation also has been reported. In an initial study in our laboratory (Smith, Dmochowski, Muir, & Kisilevsky, 2007) employing fetal heart rate obtained by a cardiotocograph, an effect of fetal HF on the fetal cardiac response in the 2 min following the offset of the mother's vs. stranger's voice was found. Using a median split of fetal HF (0.33–0.5 Hz, range restricted due to sample size), the effect was limited to the mother's voice for the group with HF above the median; there was a sustained decrease in heart rate beginning about 40 s after voice offset. To further explore this phenomenon, electrocardiographic data from the 20 pairs noted above were analyzed using a median split of fetal HF (0.4–1.7, David et al., 2007) during as well as following presentation of the mother's voice. Separate analyses during voice presentation and following voice offset revealed an effect of time [$F(119, 2142) = 2.659$, $p = 0.008$, partial $\eta^2 = 0.129$] which was linear [$p = 0.009$, partial $\eta^2 = 0.326$] during the playing of the mother's voice but, unlike Smith et al., there were no significant effects of fetal HF on fetal heart rate either during the playing of the mother's voice or following voice offset. Analyzing the data over the voice and voice offset periods combined showed a time contrast which was quadratic [$F(1, 18) = 4.705$, $p = 0.04$, partial $\eta^2 = 0.207$]. As can be seen in Figure 8.2 which includes the data during and following the voice stimulus, fetal heart rate increased during the mother's voice, the typical response reported at term (e.g., Al-Qahtani, 2005; Kisilevsky & Hains, 2011) and decreased following voice offset for both fetal HF groups. There were no differences in the prevoice period for fetal HF or time and no interactions.

Because there was a relationship between the maternal and fetal HF as well as PNS indicator during rest (see above), further analyses were carried out using a median split of maternal HF, fetal PNS and maternal PNS indicator on the fetal response during and following the playing of the mother's voice. These analyses all showed the

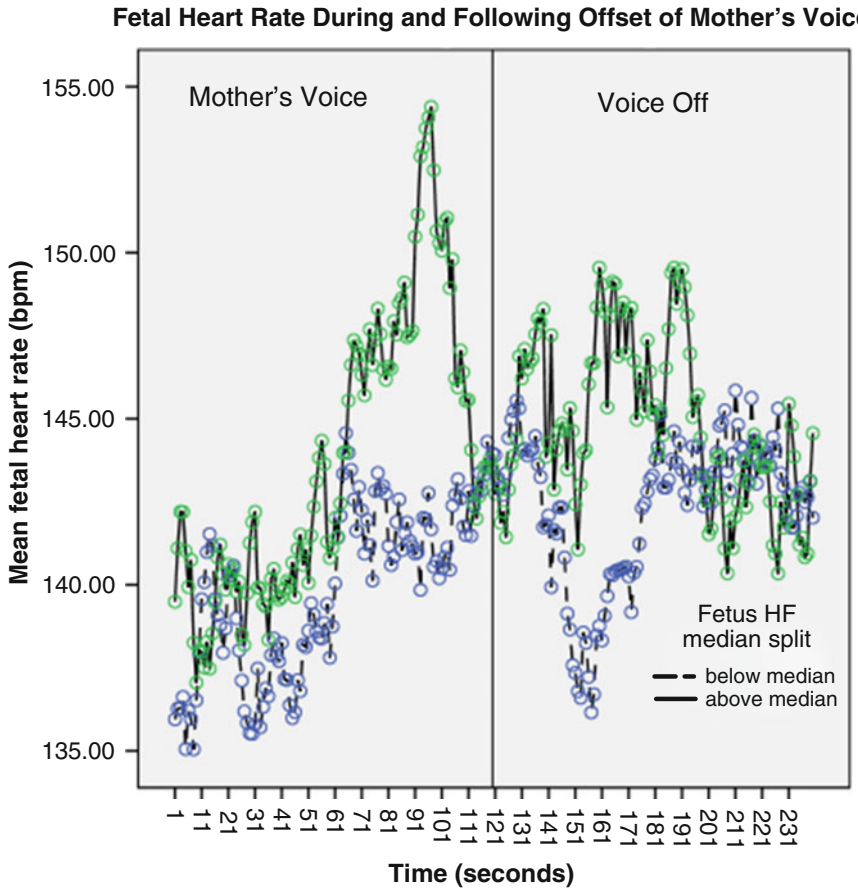

Fig. 8.2 Fetal heart rate during the playing of an audio recording of the mother's voice and following the offset of the recording for those above and below the median fetal HF shown separately

same results as the median split of fetal HF: an effect limited to time. The multiple variations in methodology (e.g., HF range, calculation of median split, recording technology) most likely account for the different findings over studies in our laboratory. Clearly, more research is needed to clarify the maternal–fetal cardiac relationship as well as the influence of sensory stimulation. Presently, fetal HR measures are obtained using diverse technologies (CTG, ECG) with HR variability parameters differing over studies (e.g., HF: 0.3–1.3, Groome et al., 1999; HF: 0.4–1.7, David et al., 2007; HF: 0.50–1.00 Hz, Signorini, Magenes, Cerrutti, & Arduini, 2003). Future standardization would ensure comparability and facilitate replicability of results.

Influence of the Uterine Environment: High-Risk Pregnancies

As well as developing a normative database of fetal perception based on data from those in low-risk pregnancies who delivered as healthy, full-term newborns, our laboratory has been interested in the influence of the 'atypical' uterine environment in high-risk pregnancies which may or may not result in a healthy, short or long-term outcome for the offspring. Positing that differential sensory elicited fetal behaviors in high- vs. low-risk pregnancies would be useful in the assessment of well-being, studies were designed to identify variations between the two populations. Early investigations employed short duration, high intensity

vibroacoustic (see Footnote 1) or acoustic stimuli. In an initial series of studies (Kisilevsky et al., 1999a, 1999b, 2001), we characterized the maturation of cardiac changes and body movement responses elicited by a vibroacoustic stimulus from 24 to 34 week GA, in high-risk fetuses threatening to deliver prematurely (hospitalized, mixed cause) as a function of newborn outcome: 39 % resulted in the term delivery of a healthy newborn; 26 % resulted in a preterm delivery of a healthy newborn; 35 % resulted in a preterm delivery with evidence of compromise (Kisilevsky et al., 1999a). Results showed differences in sensory elicited responding among the three outcome groups as well as when compared to normative data from a group of low-risk fetuses in a previous study (Kisilevsky, Muir, & Low, 1992). The high- vs. low-risk fetuses showed an earlier onset of responding to a vibroacoustic stimulus at 24 vs. 27 weeks GA but a lower magnitude of heart rate increase by 32 weeks GA. Only those high-risk fetuses who went on to deliver as healthy term newborns showed vibroacoustic elicited heart rate and body movement responses by 32 weeks GA that were indistinguishable from those of low-risk fetuses. These studies provided unequivocal evidence of behavioral differences in sensory elicited responding between high- and low-risk fetuses as a function of newborn outcome. The results could not be accounted for on the basis of maturational changes in cardiac or body movement measures occurring simultaneously with sensory development. Neither maturational changes in cardiac variables (i.e., heart rate, number of accelerations ≥15 bpm; Kisilevsky et al., 2001) nor number of ultrasound observed body movements (Kisilevsky et al., 1999b) differed in low- vs. high-risk groups when the membranes were intact. The high-risk fetuses had reduced numbers of body movements only in the presence of ruptured membranes. In a following study, a group of similar high vs. low-risk fetuses were examined using a complex airborne sound, a brief (2.5 s), high-pass filtered white noise (800–20,000 Hz), delivered in air above the maternal abdomen at three relatively loud intensity levels (100, 105, and 110 dB). The onset of hearing was determined to occur at 29 weeks GA, the same as that for low-risk fetuses. Maturation differed, however, with those high-risk fetuses who would be born at term showing an increased magnitude of cardiac acceleration (Kisilevsky et al., 2000).

Subsequently, auditory processing was examined in fetuses in high-risk pregnancies associated with placental insufficiency (e.g., maternal diabetes, hypertension, preeclampsia) vs. those in low-risk pregnancies who delivered as full-term, healthy newborns. While not a homogeneous group (i.e., conditions vary in etiology), the high-risk conditions all have the potential for insufficient oxygen and nutrient provision (undernutrition) for normal fetal growth and development, resulting in fetal/newborn growth restriction. Comparisons of responding to either a vibroacoustic or auditory stimulus also revealed differential responding in these populations. Fetuses in pregnancies complicated by maternal diabetes whether existing prior to or diagnosed during pregnancy (i.e., gestational diabetes; Allen & Kisilevsky, 1999) showed vibroacoustic induced heart rate increases and body movements, indicating that they perceived the stimulus. However, the cardiac response was less mature and less organized and as maternal blood glucose levels increased, fewer body movements were elicited. Fetuses in pregnancies complicated by maternal hypertension responded with a lower magnitude of heart rate increase, fewer body movements, and a lack of cardiac-movement coupling (Warner, Hains, & Kisilevsky, 2002). Moreover, using a brief duration, high-pass filtered white noise, a group of fetuses in pregnancies complicated by preeclampsia exhibited heart rate changes and body movement responses similar to fetuses in low-risk pregnancies (Kisilevsky et al., 2011), indicating that they heard the sound. Taken together, these results provide evidence that fetuses in high-risk pregnancies can hear. Nevertheless, the diversity in response magnitude and maturational changes in responding over gestation in the high-risk groups may indicate deviations in the processing of sounds.

In a series of studies using lower intensity, longer duration recordings of the mother's voice so as not to elicit a startle, again differential responding was evident in the presence of conditions

associated with placental insufficiency vs. low-risk. Fetuses in pregnancies complicated by well controlled gestational diabetes showed no heart rate change to their mother's voice (Kisilevsky, Gilmour, Stutzman, Hains, & Brown, 2012). Similarly, no heart rate change was found for fetuses in pregnancies complicated by maternal hypertension (Lee, Brown, Hains, & Kisilevsky, 2007) or preeclampsia (Kisilevsky et al., 2011). Moreover, in the hypertensive but not the pre-eclamptic group, a heart rate increase occurred following the offset of the mother's voice, indicating that the fetuses had heard the voice. The results of the individual studies were confirmed in meta-analyses conducted on laboratory archival data including fetuses from 23 to 41 weeks GA in high-risk pregnancies ($n=260$) complicated by threatened premature delivery, hypertension or diabetes compared with those in low-risk uneventful pregnancies ($n=233$; Kisilevsky & Hains, 2005). Because behaviors differed not only between the high- and low-risk groups but between those in the threatened preterm labour and hypertension or diabetes groups, it was concluded that the differential fetal behavior could represent adaptation to condition specific insult rather than a generalized response to insult per se. Presently, the mechanism(s) responsible for an effect of those high-risk pregnancy conditions which are associated with placental insufficiency on fetal auditory system functioning is(are) unknown and a matter of speculation.

It could be that dissimilar auditory system development, sensorineural threshold elevation, decreased iron levels and/or thyroid hormone account for the observed differential auditory processing. Diverse auditory system development has been observed in studies of animal models of placental insufficiency. Reductions in axonal diameter that are associated with slower conduction velocities (sheep, Rees et al., 1989) as well as differential brainstem responses indicating delayed myelination and/or changes in synaptic efficacy (guinea pig, Rehn et al., 2002) have been reported. In human fetuses, delayed maturation of auditory evoked responses in growth restricted fetuses was noted based on longer latencies in growth restricted vs. normally grown fetuses studied using magnetoencephalographic recordings from 27 to 39 weeks GA (Kiefer et al., 2008). Thus, it is possible that delays/diversities in system maturation account for the differential auditory responses. Moreover, animal studies showing that delays in myelination and reduction of white matter in fetuses are restored to control levels postnatally (Tolcos et al., 2011) indicate that the effects of auditory system development may be ameliorated following birth when nutrition/oxygenation are no longer compromised.

Alternatively, it could be that there is increased sensorineural threshold elevation because the magnitude of the endocochlear potential is dependent upon oxygen supply (Sohmer & Freeman, 1995). The placenta is less efficient at oxygen diffusion compared to the lungs and, in the presence of placental insufficiency, even less oxygen is being transported to the fetus. Thus, if there were decreased oxygen levels because of placental insufficiency, the intensity of the mother's voice may have been perceived as a less intense stimulus or may not have been loud enough to be consistently perceived. Clearly, fetuses in high-risk pregnancies could hear sounds because they responded to loud sounds, vibroacoustic stimuli, and in some cases, the mother's voice particularly following offset. In future studies, simply raising the intensity of the mother's voice may or may not address the threshold issue as loud sounds can elicit a startle response, confounding processing and reflexive behavior.

Structural and functional deficits in auditory processing have been reported in the presence of lower levels of iron and maternal diabetes, hypertension, and preeclampsia have been shown to compromise fetal iron stores (for a thorough review see Georgieff, 2008 and Chap. 15). Animal models have demonstrated that iron deficiency can have negative effects on myelination (e.g., Connor & Menzies, 1996), structural development of dendrites (e.g., Jorgenson, Wobken, & Georgieff, 2003), synaptic function (e.g., Jorgenson, Sun, O'Connor, & Georgieff, 2005), and brain energy metabolism (e.g., deUngria et al., 2000) which result in abnormalities in hippocampally dependent rodent behaviours (Georgieff, 2008). In keeping with these findings,

infants of diabetic mothers with low iron stores at birth (Siddappa et al., 2004) were reported to show auditory recognition memory deficits which persisted into early childhood (Riggins, Miller, Bauer, Georgieff, & Nelson, 2009). Given the relationship between iron stores and auditory recognition memory, it may be possible to use newborn ferritin levels to determine an effect of iron stores in future studies examining fetal auditory processing.

Level of thyroid hormone also may play a role in differential auditory responses given that cochlear structures are sensitive to the morphogenetic effect of thyroid hormone during the whole duration of maturation (Uziel, 1986). Growth restricted fetuses have been reported (Kilby et al., 1998; Kilby, Gittoes, McCabe, Verhaeg, & Franklyn, 2000) to have reduced circulating levels of free thyroxine (T4), triiodothyronine (T3), and reduced expression of α and β isoforms of thyroid protein. As well as ferritin, it would seem prudent in future studies to measure newborn thyroid levels to examine the effect on auditory processing.

Overall, it may be that disparate auditory system development, sensorineural threshold elevation, decreased iron levels and/or thyroid hormone, individually or in some combination, account for the differential auditory processing observed in the high-risk fetal groups studied. Given that all of these issues can be redressed after birth when increased nutrient and oxygen supplies become adequate for normal growth, environmental sounds are no longer attenuated by the maternal abdomen and tissues, and oxygenation improves with lung diffusion, it is important that future studies determine their role and the short- and long-term persistence of effects.

Fetal Auditory Processing: Influence on Language Development

Given (1) differential fetal response to sounds in high-risk pregnancies associated with placental insufficiency which, in turn, are associated with fetal growth restriction and (2) a 30-year history of follow-up studies reporting an increased risk for language deficits in infants born growth restricted (e.g., 2–5 years—Gutbrod, Wolke, Soehne, Ohrt, & Riegel, 2000; Low et al., 1982; Vohr, Garcia Coll, & Oh, 1988;Walther & Ramaekers, 1982; 5–9 years—Chaudhari, Bhalerao, Chitale, Pandit, & Nene, 1999; Korkman, Liikanen, & Fellman, 1996; 9–11 years—Low et al., 1992), we hypothesized (Kisilevsky & Davies, 2007) that fetal growth restriction affected auditory system development, resulting in atypical auditory information processing in growth restricted vs. appropriately grown fetuses and that speech perception which lays the foundation for later language competence would differ and be associated with later language abilities.

Recently, we reported support for this hypothesis (Kisilevsky, Chambers, Parker, & Davies, 2014). In a longitudinal study, we compared auditory information processing in growth restricted (≤10 percentile, weight for gestational age) vs. appropriately grown fetuses and newborns and assessed neurodevelopment and language in the two groups at 15 months-of-age. As fetuses, the growth restricted group, in contrast to the appropriately grown group, showed a less sustained response to their mother's voice (1 min vs. 4 min in low-risk fetuses). As newborns, again in contrast to the appropriately grown group, they showed no preference for their mother's vs. a female stranger's voice and less recovery to a novel word following habituation. At 15 months, fetuses in the growth restricted group showed expressive language deficits, scoring more than 2 standard deviations below the mean of the appropriately grown group on both the Mullen Scales of Early Learning Expressive Language Subscale and the MacArthur-Bates Communicative Development Inventory Early Word Vocabulary Produced subscale. These results could not be attributed to neurodevelopment in general because, except for the one subscale, similar to the infants who were appropriately grown, the growth restricted infants scored average or above average on all other Mullen subscales (gross motor, fine motor, visual receptive, receptive language). While correlational analyses does not prove causation, the con-

sistency in differential auditory processing observed in a relatively small sample of growth restricted fetuses which persisted into the newborn period and was associated with later expressive language deficits very early in development clearly indicates that this is an avenue of research which is critical to pursue. Language impairments have been associated with numerous clinical disorders that manifest in cognitive (e.g., executive function, Henry, Messer, & Nash, 2012; working memory, Hutchinson, Bavin, Efron, & Sciberras, 2012), social (e.g., autism spectrum disorders, Joshi et al., 2013), emotional (e.g., anxiety disorder, Beitchman et al., 2001), and behavioural (e.g., attention deficit/hyperactivity disorder, Helland, Biringer, Helland, & Heimann, 2012) dysfunction and can have a profound effect on an individual's everyday functioning, academic achievement and occupational status (Johnson, Beitchman, & Brownlie, 2010). Thus, in future studies, it would be important not only to recruit larger sample sizes to begin to identify individual fetuses and newborns at greatest risk for subsequent language deficits but also to begin to test interventions such as systematic presentation of audio recordings of the mother's voice to at-risk fetuses and/or newborns. The latter suggestion is already showing positive results in premature infants (e.g., Krueger, Parker, Chiu, & Theriaque, 2010; Rand & Lahav, 2014) and could have the potential to prevent and/or ameliorate such deficits.

Overall Summary and Conclusions

In summary, this chapter reflects a historical perspective on the study of fetal sensory sensitivity over the past 35+ years. By the start of the third trimester of pregnancy, observations of reliable auditory elicited startle responses (i.e., immediate body movement, increase in heart rate within 5 s) signal fetal hearing and the opportunity for environmental sounds to influence the shaping of neural networks which lay the foundation for later language learning. Subsequently, over gestation, fetuses discriminate speech sounds, voices, and languages. The mother's audio-recorded voice seems to be a particularly salient stimulus. Without training, at term, low-risk fetuses who deliver as healthy, newborns respond during the playing of her voice with a heart rate increase while to other voices, including a female stranger's or the father's, they either do not respond, respond with a heart rate decrease or show an offset response. The mother's voice is a ubiquitous sound to which they would be exposed every time that she speaks. The differential response suggests that repeated exposure sets up some neurological modification that ultimately leads to memory for her voice. Given the importance of the symbiotic relationship for fetal development, the effect on auditory processing of the maternal–fetal heart rate relationship and 'atypical' uterine environments observed in high-risk pregnancy populations were examined. Although relationships were found between maternal and fetal heart rate and heart rate variables, none were found to influence auditory processing in low-risk populations. As well, auditory processing was compared in fetuses in low- and high-risk pregnancy populations. Fetuses in all high-risk groups studied (i.e., threatening premature delivery, diabetes, hypertension, preeclampsia, growth restriction) showed differential responding to a vibroacoustic stimulus, filtered white noise, and/or the mother's voice compared to fetuses in low-risk groups. The reason for the observed differential responding is a matter of speculation at this time. It could be that dissimilar auditory system development, sensorineural threshold elevation, decreased iron levels and/or thyroid hormone between low- and high-risk populations account for the observed differential auditory processing. Importantly, it is possible that the observed differences are predictive of future language abilities. Our short-term follow-up of fetuses identified as growth restricted in utero (confirmed at birth) who demonstrated differential auditory information processing revealed expressive language deficits at 15 months of age. Clearly, future research is necessary to identify individual fetuses and newborns at greatest risk for subsequent language deficits. Testing interventions which have the potential to prevent and/or ameliorate such deficits is imperative as the negative

cognitive, social, and emotional dysfunction associated with communication impairments can have a profound effect on an individual's everyday functioning, academic achievement and occupational status.

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