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Autonomic Control of Fetal Cardiac Activity

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INTRODUCTION

Substantial differences between fetal and adult circulation need to be reviewed briefly before the autonomic control of fetal heart action can be discussed. This includes the anatomical communication between the left and right heart, which provides for a parallel circulation, substantially bypassing the pulmonary circulation. Since 60% of the blood from the right ventricle passes through the ductus arteriosus,[1] it can be deduced that the autonomic nervous system exerts a significant control over circulation and hence activity of the heart. The left ventricle of the fetus principally perfuses the myocardium and the central nervous system (CNS), whereas the right ventricle through the ductus arteriosus perfuses the descending aorta and distal organs.[1] Thus, even though the two ventricles function hemodynamically in parallel, the flow of oxygenated blood differs in its final distribution. Per unit of body weight, the cardiac output of a fetus is higher than that of an adult.[2] The fetus controls the partial pressure of oxygen in its blood mainly through its own chemoreceptors. The most important are the chemoreceptors of the aorta, which are extremely sensitive to changes in oxygen level and which initiate the various hypoxia control mechanisms.[3] Hypoxia initially induces the tachycardia and an increase in arterial pressure mediated by catecholamines, ACTH, and vasopressin.[4] When hypoxia increases beyond a critical level of about 16 mmHg partial oxygen pressure, bradycardia results.[5] This probably occurs through a vagal response mediated by the chemoreceptors of the aortic arch and bulb. A redistribution of blood flow is observed as a result of the decrease in partial oxygen pressure. The secretion of catecholamines increases the afterload on the right ventricle. As a consequence, an

increased right, and therefore also left, atrial diastolic blood residue accumulates and the diastolic atrial pressure increases. This in turn increases the left ventricular preload and hence perfusion of critical areas such as the myocardium and brain. The redistribution of blood flow is also facilitated by the decrease in vascular resistance in the central circulation which is caused by the effect of hypoxia on the vessels of the brain.[6]

The uterine-placental and umbilical circulations largely determine the development of the fetus.[7–9] It has long been known that the umbilical circulation absorbs more than 40% of the fetal cardiac output.[10] However, only recently has it become possible to evaluate resistance in these vessels throughout gestation. Doppler flow studies have shown, in vivo, that vascular resistance decreases progressively during the course of gestation[11] (see also Chapter 42). Concomitantly, the uterine arteries show a progressive increase in the diastolic component of the velocimetric curve. By the end of gestation the resistance in the uterine arteries is so low that systolic and diastolic velocities appear similar.[7] The velocity of flow in the fetal aorta does not change in parallel in normal pregnancy.[12]

The fetal heart rate is also very different from that of the adult. Because of the need to maintain a relatively high cardiac output, which ensures adequate blood flow, the fetal heart rate is higher than that of adults. Romanini et al.,[13] in studying the fetal heart rate over the course of a pregnancy, noted statistically significant differences in the slopes of regression lines, calculated for the periods before and after the 14th week (Fig. 36.1). This observation opens the door to different hypotheses concerning mechanisms that control the fetal heart rate during different phases of gestation. From these short introductory notes, it must be clearly understood that all the mechanisms described above do not operate independently, but are closely linked in an array of complex relationships often not yet fully understood. For a more detailed discussion of the anatomy, hemodynamics, and other physiologic parameters of the fetal heart, the reader is referred to Chapters 35 and 44.

AUTONOMIC SYSTEM

As in the adult, the heart beat in the fetus originates in the sinoatrial node. Following spontaneous depolarization of pacemaker cells, the electrical impulse spreads through the right and left atrium (start of atrial systole), along a specialized tract of the atrioventricular (AV) node, and from there to the branches of the bundle of His and the Purkinje fibers (ventricular systole).

The chronotropic activity of the sinoatrial node is under the influence of the autonomic nervous system. The frequency of the impulses from the sinoatrial node increases when the sympathetic impulse prevails and decreases when the parasympathetic impulse prevails. Acetylcholine increases the permeability to K^+ of the cellular membrane in the pacemaker cells, leading to an increase in the flow of K^+ to the extracellular space, with a consequent increase in the resting potential. Catecholamine, on the other hand, reduces the flow of K^+ towards the extracellular space, leading to a decrease in the resting potential and an increase in the frequency of depolarization.

Development of the Parasympathetic System

The parasympathetic innervation of the heart originates from the cardiac branches of the vagus nerve which originate from the recurrent laryngeal nerves and the thoracic vagi immediately distal to them. These nerves are interconnected with the heart nerves of the sympathetic system, forming dorsal and ventral cardiopulmonary plexuses in the mediastinum at the base of the heart. The dorsal plexus is located dorsal to the aortic arch and pulmonary artery. The smaller ventral plexus is located anterior to the aorta and pulmonary artery. These plexuses are the origin of the right and left coronary cardiac nerves and the left lateral cardiac nerve which, together with other small nerves originating from the plexuses and the thoracic vagi, innervate the heart.[14]

Ontogenetic development of parasympathetic innervation of the heart has been studied mainly in the chick embryo since

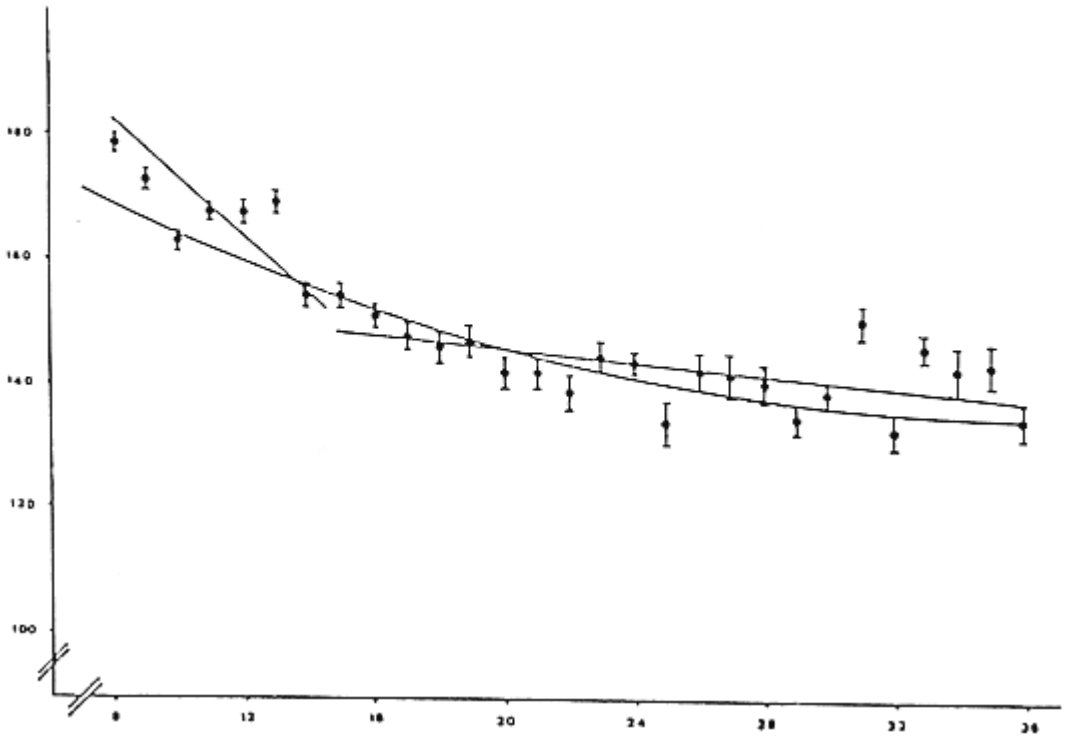

Fig. 36.1. Fetal heart rate during the course of pregnancy. The curve showing the general trend and the two regression lines calculated for experimental values before and after the 14th week are shown. The difference between the slopes of the two lines is statistically significant.[14]

the human heart and the chick heart have similar characteristics during the early stages of development.[15] In the human embryo, development of vagal innervation starts in the early days of the 8th week of gestation.[16] By about the 10th week, nerve fibers from the right vagosympathetic trunk invade the aorta, the veins, and the pulmonary artery.[17] Vagal innervation is complete by about the 12th week in the atria and the 13th week in the ventricles.[16] The first ganglia cells appear at about the 8th week between the aorta and the pulmonary artery. Later, at the 13th week, the gangliar structures seem to be concentrated in five main groups in the regions to the upper rear of the atria, the interatrial sulcus, the arterioventricular sulcus, and in the tunica adventitia at the roots of the aorta and the pulmonary artery.[16] In the 120-mm fetus, irregular cells with the morphological features of mature ganglia cells can be seen first.[18] The process of expansion and spread of the ganglia continues up to about the 34th week of gestation.[19]

The origin and development of the functional activity of the parasympathetic nervous system have been studied with field stimulation at the gestational ages of 12 and 20 weeks.[20] This method involves the release of neurotransmitters by present myocardial autonomic nervous structures. Their effects can be evaluated from changes in tension of the myocardial tissue. A decrease in tension (negative inotropic effect) is caused by release of acetylcholine.

Before the 13th week of gestation, no responses to stimulation are observed. This suggests an immature autonomic nervous system. Subsequently, a response can be observed which, on the whole, is more frequently of the cholinergic than the adren-

ergic type. The inhibitory effect, produced by acetylcholine, appears present even before autonomic innervation of the heart has developed. A negative chronotropic effect on the sinoatrial pacemaker can already be observed from the 7th–10th weeks of gestation.[20,21] In contrast, nicotine does not appear to cause any appreciable inhibitory effects.[20] This suggests the absence of gangliar nicotine receptors up to the 20th week of gestation. Since ganglia may be functionally immature up to the 20th week of gestation, vagal transmission to the heart may not take place. Schifferti and Caldero-Barcia[22] demonstrated in vivo an increase in vagal effect on fetal heart rate with progress of pregnancy. Administration of atropine to pregnant women between the 15th–40th weeks of pregnancy blocked vagal control, causing an increase in fetal heart rate as pregnancy progresses from 5 beats per minute at 15 weeks to 20 beats per minute at 40 weeks. This work suggests that the progressive decrease in fetal heart rate from the 4th month of pregnancy on may be the result of a progressive increase in vagal tone.

Development of the Sympathetic System

The sympathetic innervation of the human heart originates from the stellate ganglia and the caudal halves of the cervical sympathetic trunks below the level of the cricoid cartilage. As already mentioned, these nerves link up with the parasympathetic nerves at the level of the ventral and dorsal cardiopulmonary plexuses, located anteriorly and posteriorly to the pulmonary artery from which the heart nerves take their origin.[14] The most complete studies on the ontogenesis of the sympathetic innervation of the heart have once again been carried out on the chick.[15] They primarily have been based on the identification of catecholamine by histochemical fluorescent methods.[23] Some disagreement remains since some studies have claimed the absence of fluorescent nerve trunks from the 8th–18th weeks of gestation.[24] Others[25] have indicated the possible presence of intracardial nerve trunks by demonstrating a low level of fluorescence between the 10th–16th weeks of gestation. No such disagreement exists later, when between the 13th–23rd weeks fluorescent nerve structures can be demonstrated uniformly. These appear denser in the atria than in the ventricles.[26]

In contrast to this late appearance of innervation, the human fetal heart is able to synthesize norepinephrine from the 13th week of gestation.[21] Since sympathetic nerve terminals in the heart are absent and only small cellular fluorescent formations appear present, it has been suggested that during early stages of development sympathetic control is effected through humoral rather than adrenergic nerve mechanisms.[24,25]

The presence of beta-adrenergic receptors in the human heart between the 12th–22nd weeks of gestation has been demonstrated utilizing the fact that fetal atrial tissue is more sensitive to isoproterenol than to norepinephrine.[27] The start of functional development of adrenergic neuroeffector transmission has been studied by field stimulation of atrial tissues in embryos between 12–20 weeks old.[20] Using this method, a postitive inotropic effect has been noted from the 13th–14th weeks of gestation on. This effect is increased by drugs such as phenoxybenzamine which block neural uptake of noradrenaline and is decreased by drugs such as propranolol which block beta-receptors. The involvement of noradrenaline in the positive inotropic response produced by field stimulation therefore appears likely.[20]

As stated earlier, the greater frequency and earlier presence of cholinergic responses in these experiments suggest that the functional activation of the parasympathetic system occurs slightly ahead of the sympathetic system. High doses of nicotine produce an excitatory effect that is blocked by propranolol.[20] This effect is therefore presumably due to the release of noradrenaline. Since nicotine provokes release of noradrenaline from both the sympathetic neurons and chromaffin tissue, and since an excitatory response in an embryo of about 8 weeks (prior to the appearance of the normal response to field stimulation) has been observed,[20] it has been suggested that in

the early stages of fetal development the chromaffin tissue may be the principal site for release of noradrenaline, even before sympathetic transmission is established.

Sympathetic and Parasympathetic Control of the Fetal Heart and Circulation

The inhibitory effect of vagal activity on the heart opposes the facilitory influence of sympathetic activity. Differing results have been obtained in research on animals, specifically on chronically instrumented fetal sheep.[28] In this study, aimed at determining the importance of autonomic nervous system control on the fetal heart rate, Assalie et al.[28] demonstrated that atropine blockage of the cholinergic receptors resulted in a significant increase (10%) in heart rate, but only in fetuses at term. In premature and immature fetuses, the increase was less significant (2% and 4%, respectively). In contrast, propranolol blocking of beta-adrenergic receptors produced a more marked effect, decreasing the heart rate by 10% in immature fetuses, 12% in premature fetuses, and 14% in those at term. These data show that the sympathetic system predominates in control of heart rate in sheep fetuses. The parasympathetic system only begins to play in important role near term. This role then becomes even more marked in the neonatal period.

The simultaneous blocking of cholinergic and beta-adrenergic receptors decreases the fetal heart rate and thus confirms the predominance of the sympathetic system in control of fetal heart rate. In the neonatal stage, the situation is reversed. The same dual blockage causes a marked increase in heart rate, as would be expected from a predominance of the parasympathetic system.

Since the two parts of the autonomic nervous system are tonally active, account must be taken of the fact that the opposite effects of the sympathetic and parasympathetic systems are not summed algebraically. In animal studies, in particular, it has been noted that the response of the heart rate to a given level of vagal stimulation varies substantially according to the prevalence of sympathetic activity.[29,30] Levy[31] defines this exaggerated vagal inhibitory response to the increase of sympathetic tone as "accentuated antagonism". At the sinoatrial node level, the effect of sympathetic activity is progressively attenuated as the level of vagal activity rises. This occurs through the inhibitory effect that the acetylcholine, liberated by the vagal terminates, exerts on the release of norepinephrine via the contiguous sympathetic terminals.[30] How this interaction between the sympathetic and parasympathetic systems takes place and how it effects the autonomic control of the fetal heart are still unknown.

Turning to the control of the circulation by the autonomic nervous system, it appears that a progressive increase in neurohumoral control over the peripheral circulation occurs with advancing gestation. This turns out to be exerted to a markedly greater degree by the alpha-adrenergic system than by gangliar structures.[32,33] This neurohumoral control reaches a peak at term and then decreases progressively during the neonatal period.[28] In contrast, the parasympathetic system plays a markedly dominating role in control of the pulmonary circulation and of the blood flow through the ductus arteriosus.[34]

RECEPTOR SYSTEM

Baroreceptor Reflex

There are contradictory data in the literature on the increase of the baroreceptor response during the course of pregnancy. Such an increase has been encountered by some authors[35] and denied by others.[36,37] The part played by the autonomic nervous system in baroreceptor control has been studied by Ismay et al.[37] in chronic fetal sheep preparations. Using phenylephrine to induce a sharp increase in arterial pressure, it was observed that the baroreceptor reflex was abolished by atropine and increased by propranolol. This response shows that the activity of the baroreceptor response depends on parasympathetic control

and is inhibited by the sympathetic system. An increase in the sensitivity of the baroreceptors has been observed in adult rabbits when alpha-receptors are blocked.[38]

It seems, however, that chemoreceptor systems—which are extremely sensitive to changes in the partial oxygen pressure—rather than baroreceptor systems, represent the predominant systems that control fetal hemodynamics. In the condition of fetal stress, the release of catecholamines into the bloodstream and their action on alpha-adrenergic vessel receptors appear to represent the main stimulus for the selective redistribution of blood flow, which is observed in hypoxia (vasodilation in the coronary, cerebral, and umbilical circulations and vasoconstriction in the visceral, lung, muscle, and cutaneous zones[39]).

Chemoreceptor Reflex

Walker et al.[40] have demonstrated that the response to hypoxia in chronic fetal sheep preparations depends on gestational age. In fetuses before 0.8 of term gestation, hypoxia produces a modest increase in blood pressure but does not cause significant changes in heart rate. In the fetus after 0.8 of term gestation, one observes bradycardia and an increase in blood pressure. The roles of the parasympathetic and sympathetic systems in these responses were also evaluated by Walker et al.[40] Before 0.8 of term gestation, it was observed that hypoxia gave rise to a balanced increase in sympathetic and parasympathetic activities before any significant effect on the fetal heart rate occurred. After 0.8 of term gestation, there was a predominant increase in parasympathetic activity superimposed on a concomitant but less effective increase in sympathetic activity, with bradycardia appearing as a result.

The chemoreceptor response to changes in fetal homeostasis has also been analyzed in a number of studies on fetal sheep preparations in which changes in fetal PO_2, PCO_2, and pH occurred by: 1) altering maternal inspiratory gas tension by administering mixtures of varying composition; 2) provoking occlusions of the maternal common internal iliac artery; and 3) provoking compression of the umbilical cord in toto or either umbilical veins or arteries separately.

Initially, in the presence of a modest decrease in PO_2 and an increase in PCO_2, one observes a bradycardia that can be considered to be of chemoreceptor origin and appears mediated by the vagus. Once a significant increase in blood pressure appears, bradycardia persists but seems to be caused by simultaneous chemo- and baroreceptor stimulation in response to the increase in afterload, provoked by the peripheral vasoconstriction and mediated by the adrenergic nervous system. When hypoxia and acidosis persist, the initial bradycardial response may be followed by an increase in fetal heart rate, provoked by an increase in myocardial contractility due to increased release of adrenal catecholamines. However, when hypoxia and acidosis exceed a critical level, a predominant vagal activity is imposed on the increased sympathetic tone. This results in the appearance of bradycardia aimed at saving glycogen reserves, especially those of the myocardium, in an attempt to keep the fetus alive.

HEMODYNAMIC CONTROL

Changes in cardiac output may be caused by changes in heart rate (*chronotropic effect*) or in the force of the contractions (*inotropic effect*) through the control exerted on the heart by its sympathetic and parasympathetic innervation. The energy of contraction is also proportional to the length reached by the myocardial fibers in the preload diastolic phase (*Frank-Starling law*). The fetal heart, however, behaves differently than the heart of an adult (see Chapters 1 and 3). The autonomic nervous system plays a fundamental role in the maintenance of physiologic cardiocirculatory conditions and in the reactions of the fetal cardiocirculatory apparatus to conditions of fetal stress.

The fetal lamb was used successfully by Dalton et al.[41] to demonstrate the interaction of the β-sympathetic (cardioacceleratory) and parasympathetic (cardioinhibitory) systems under known physiologic

conditions. Dalton et al.[41] used drugs with blocking actions on the two systems, administering the minimum doses needed to obtain complete blocking. The response was evaluated, measuring mean heart rate and heart rate variability, measured as the *mean beat-to-beat difference (MABB)* for the highest frequencies and as the root mean square deviation (2 MSD) of R-R intervals for lower frequencies. Atropine, which blocks the action of acetylcholine, liberated by postganglionic parasympathetic nerves, was used as a blocker. The heart rate increased rapidly, but the MABB fell. No differences dependent on gestational age were observed. No changes in either blood gases, hematocrit, or blood pressure were noted. There was, however, some reduction in respiratory movements. This probably related to the central action of atropine which causes a prolonged episode of high-voltage electrocortical activity[42] and reduces respiratory activity. Atropine reduces the MABB much more significantly than the 2 MSD. This makes one think that high-frequency variability is more influenced by the parasympathetic system. Use of the selective blocking agent propranolol rapidly reduced the heart rate, but did not influence either MABB or 2 MSD. No significant change occurred in blood gases, hematocrit, blood pressure, or breathing activity. If atropine is added to propranolol, variability is greatly reduced, clearly demonstrating that variability is the result of a push-pull relationship between the two components of the autonomic nervous system. Phentolamine, a sympathetic blocking agent, caused a slow rise in the heart rate and MABB and 2 MSD increased significantly. This fact was accompanied by a small fall in arterial pressure.

In order to establish which CNS structures are responsible for normal beat-to-beat variability, one has to refer to animal studies. In fetal lambs, if the brain is destroyed but the spinal cord is left intact up to and through the cervical region, the heart rate tracing becomes "flat". If, however, the brain stem is transected on its upper parts, heart rate variability remains normal.[42]

The effects of adrenergic and catecholamine stimulation on the fetal heart rate have already been discussed. At this point it should be added that circulating catecholamines, and in particular adrenaline, can also produce effects that are not mediated by nerves but by endocrine action. Although noradrenaline seems to be the predominant catecholamine in fetal life,[43] all circulating catecholamines may be liberated under different stimuli and in consequence influence the fetal heart rate.[44] The medulla of the fetal adrenal gland seems to be able to react to anoxia independently of the CNS.[45]

Jones and Robinson[46] have shown that in the catheterized lamb, fetal hypoxia was followed by an increase in adrenaline and noradrenaline in the circulation. The first consquence was an increase in arterial pressure, followed by a reduction in heart rate which, however, soon returned to normal levels. When hypoxia was induced by acute maternal hemorrhage,[45] bradycardia again appeared together with hypertension and a rise in the differential pressure. The heart rate soon returned to normal. This response is similar to the response towards baroreceptor stimulation. These studies suffer from the fact that the response to catecholamines is "impure" when it is obtained through anoxia. Vapaavouri et al.[32] established that the fetal heart differs from that of the adult in its response to adrenergic stimulation. The tachycardial response is less evident in the fetus than in the adult. In contrast, norepinephrine provokes a greater response in the fetus than in the adult.[46] It is also probable that there are differences in the concentrations and interactions of adrenergic receptors.

In evaluating the activity of the fetal adrenal and the resulting control over the fetal heart, one faces the problem of differentiation between the production of catecholamine by the mother and/or the fetus. For a long time it was thought that the fetal and maternal systems were separate, with no transplacental transfer occurring.[44] Chen et al.,[47] however, suggested that a catecholomethyl-transferase, which denatures catecholamines on passage across the placenta, exists. Other studies [48–50] conclude that transfer of maternal catecholamines to the fetus takes place to a limited extent

only, and does not exceed 20% of the original maternal concentration. If we accept the validity of these observations, we must conclude that the maternal sympathetic system exerts great influence on the fetal adrenal sympathetic system and its cardiocirculatory activity.

As has already been said, during the course of fetal life there is a continuous change in the response to adrenergic stimuli. [32,46] It has also been demonstrated that the response to catecholamines is modified by thyroid hormones. [51,52] These observations suggest that thyroid hormones exert a permissive action on the beta-adrenergic activity of receptors in the fetal heart. Dipak[53] demonstrated that thyroid activity is mediated through an increase in the number of β-adrenergic receptor binding sites.

The opioid peptides are produced by the fetal hypophysis and there predominantly by the intermediate lobe.[54] This portion of the hypophysis is particularly prominent in the fetus. No adequate studies are in the literature which address the effect of opioids on the activity of the fetal heart. In the adult, opioids produce hypertension and bradycardia by decreasing sympathetic while increasing vagal tone at the autonomic nuclei of the brain stem.[55] An increase in opioid levels in plasma[56] and amniotic fluid[57] has been noted to be associated with fetal distress, abnormal heart rate patterns, and acidosis. To demonstrate a depressive action of opioids on fetal heart activity, a specific antagonist (naloxone) has been administered to fetuses, resulting in improvement in beat-to-beat variability.[58]

Maternal and fetal opioid levels have recently been correlated through the secretion of cortisol, a hormone that passes freely through the placential barrier and acts as an inhibitor for the synthesis of pro-opiomelanocortine.[59]

In order to investigate whether fetal and/or maternal gland suppression induces effects on the fetal cardiac pattern, we administered triancinolone to five healthy pregnant women at 35 weeks of gestation. Five patients of the same gestational age served as controls. Fetal heart rate and fetal movements were recorded continuously over 24 hr by cardiotocography. After week three (38 weeks of gestation), the recordings were repeated without drug administration. Cortisol, adrenocorticotropin hormone, estradiol-17/3, and unconjugated estriol were contemporaneously measured in maternal peripheral plasma every 2 hr. At 35 weeks, we noted the loss of circadian rhythms of the investigated hormones. In addition, fetal heart rate patterns differed in the treated groups from those in the control group. No differences in either hormonal biophysical parameters were found in the two groups after the end of the treatment. These data suggest that the inhibition of fetal and maternal adrenal glands may cause changes in fetal heart rate patterns.

The mechanism that regulates changes in fetal behavioral states is still unknown. Walker et al.[60] suggested that such changes could be related to diurnal variations of uterine blood flow. Nathanielsz et al.[61] proposed entrainment of a periodicity of fetal behavior by a sensory pathway caused by the pressure of uterine contractions of the fetal body. We have previously hypothesized that fetal behavior may be influenced by maternal plasma cortisol levels.[62] Visser et al.[63] also noticed that the fetal heart rate resembles that of maternal plasma cortisol variations.

One of the most interesting aspects of fetal heart rate activity relates to the action of prostaglandins since they are involved in the control of the ductus arteriosus.[64] Because of its relaxing action on the pulmonary circulation,[65] PGE_2 has been used in an attempt to treat pulmonary hypertension in neonates.[66]

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