EXPERT REVIEWS

New insights on fetal ductal constriction: role of maternal ingestion of polyphenol-rich foods

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Fetal ductus arteriosus constriction is a clinical disorder that occurs as a result of inhibition of the prostaglandin synthesis pathway, and has long been associated to maternal intake of nonsteroidal anitiinflammatory drugs in late pregnancy. As a consequence of an increased right ventricular pressure, with tricuspid regurgitation and heart failure, there is a risk for the development of neonatal pulmonary artery hypertension. This artcile reviews the basic knowledge of the mechanisms involved in this important disorder. Clinical and experimental evidence that maternal consumption of polyphenol-rich substances, such as herbal teas, orange and grape juice, chocolate, and others, may interfere with fetal ductus arteriosus dynamics are discussed. Preventive measures to avoid fetal ductal constriction in the third trimester of pregnancy are discussed, including the possible need to change maternal dietary orientation, aiming to limit ingestion of foods with high concentrations of polyphenol-rich substances.

Keywords: ductal constriction • echocardiography • fetus • prostaglandins • pulmonary hypertension

Ductus arteriosus in the fetal & neonatal period

During fetal life, the ductus arteriosus, as a result of the high pulmonary resistance, directs 75–85% of the right ventricular output from the superior vena cava, coronary sinus and a small portion from the inferior vena cava to the descending aorta, distal to the origin of the left subclavian artery – the aortic isthmus [1]. Functional ductal closure is initiated by a higher blood oxygen level. This mechanism, although mediated by prostaglandins and endothelins, is intrinsic to smooth myocardial cells. It is a potentially reversible event that occurs 8–72 h after birth, as a result of muscular constriction. After this period, there is permanent closure of the ductus, characterized by the formation of the arterial ligament [2].

Constrictive & relaxing factors upon the ductus arteriosus

Since it possesses a predominant muscular layer, ductus arteriosus closure is influenced by a number of relaxing and constricting factors. Relaxing factors include prostaglandins, nitric oxide and bradykinin, which cause the liberation of prostaglandins and nitric oxide. Constrictive factors are oxygen, high levels of bradykinin, and sympathetic and parasympathetic nervous system activity [3,4]. With increase in gestational age, the ductus arteriosus becomes less sensitive to dilating effects and more sensitive to constrictive factors [5,6]. The production of prostaglandins is due to the presence of two enzymes that act on different stages: cyclooxygenase (COX)-1, which is expressed constitutively, and COX-2, whose production is locally induced during inflammatory processes [7].

As for substances with a constrictive effect upon the ductus arteriosus, indomethacin, a COX inhibitor used in the treatment of premature labor, is one of the most extensively studied [8,9]. Fetal ductal constriction may occur in the first hours of its administration and its action may last for weeks [10–12]. Ductal sensitivity to indomethacin increases with gestational age, with constriction occurring in 5–10% of fetuses below 27 weeks and in nearly 100%

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above 34 weeks, in various degrees of severity [13,14]. In addition to indomethacin, several other nonsteroidal anti-inflammatory drugs have been shown to have a constrictor effect on fetal ductus arteriosus, such as nimesulid, diclophenac, aspirin, matamizol and ibuprofen, among others [15,16].

Glucocorticoids also have an influence on ductus arteriosus patency. Like the great majority of other anti-inflammatory drugs, glucocorticoid effects on the ductus arteriosus are dose dependent [17]. In addition, when associated with nonsteroidal anti-inflammatory drugs, selective or not to COX, glucocorticoids have a synergistic effect that significantly increases the frequency and severity of ductal constriction, possibly as a result of its ability to decrease ductal sensitivity to prostaglandins [18].

Other substances tested experimentally with a proven constrictor effect upon the fetal ductus arteriosus in rats are retinoic acid, prostanoid EP4 receptor antagonists and inhibitors of nitric oxide syntesis (L-NAME), the latter with a human effect already demonstrated [19–22]. Recently, a novel mechanism of sustained ductal constriction induced by oxygen was found, secondary to activation of the enzyme Rho-kinase [23]. Thus, inhibition of this enzyme could be an important research field in the attempt to find new substances capable of sustaining postnatal ductal patency.

Premature constriction of ductus arteriosus: diagnosis, clinical aspects, natural history & treatment

For almost 40 years, it has been speculated that ductal constriction is responsible for an increase in the pulmonary artery muscular layers and consequently an increase in pulmonary vascular resistance during fetal life. It was long postulated that a pathogenetic mechanism to the development of persistent pulmonary hypertension in the neonate was related to constriction of fetal ductus arteriosus [24]. Experimental studies in the present era have demonstrated that premature constriction of ductus arteriosus during fetal life causes hemodynamic repercussions that may be associated with vasoconstriction of pulmonary arterioles and to pulmonary hypertension. For this reason, fetal ductal constriction is being used as the experimental model of choice of fetal pulmonary hypertension in the vast majority of studies aimed to increase clinical and therapeutic knowledge of this disorder [25]. The higher resistance in the ductus causes turbulence of blood-flow, with an increase in systolic and diastolic flow velocities and decrease in ductal pulsatility index. As a consequence, there is dilatation of the pulmonary artery trunk, right atrium and right ventricle, tricuspid regurgitation, pulmonary valve insufficiency, and right ventricular systolic and diastolic dysfunction [8,26]. Clinically, the fetus may be asymptomatic or show signs of heart failure, hydrops and even intrauterine death [26].

Echocardiographic criteria for fetal ductal constriction include the presence, at color Doppler, of a turbulent flow in the ductus arteriosus, with a maximal systolic velocity higher than 1.4 m/s, a maximal diastolic velocity higher than 0.3 m/s and a pulsatility index lower than 1.9 (Figure 1) [27]. This last parameter is being changed to a cut-off point of approximately 2.1. In patients with total occlusion of ductus arteriosus, the absence of ductal flow is diagnostic.

With the increase in afterload secondary to ductal constriction, there is early proliferative growing of the heart muscle, but later hyperplasia gives place to apoptosis and a hypertrophic response [28]. Systolic and diastolic functions are impaired, with an abnormal tricuspid E/A ratio, increased right ventricular Tei index and decreased ventricular shortening fraction [29–31]. As for the hemodynamic compromise, it is considered mild when there is mild tricuspid and/or pulmonary regurgitation and no right ventricular dilatation, moderate in the presence of tricuspid regurgitation with right ventricular dilatation but no hypertrophy and/or contractile dysfunction, and severe in the presence of important tricuspid or pulmonary insufficiency, functional pulmonary atresia, increase in right atrial and ventricular chambers with ventricular hypertrophy and/or systolic right ventricular dysfunction, usually with bulging of the interventricular septum from right to left (Figure 2). Other signs that are considered severe are those with complete ductal occlusion, fetal hydrops and, alternatively, when the pulsatility index is lower than 1.0, independently of other manifestations [31,32].

Even when ductal constriction is severe after maternal usage of prostaglandin inhibitors, cessation of its consumption is usually followed by a decrease in systolic and diastolic velocities, with an increase in pulsatility index, and a gradual improvement of hemodynamic alterations. In some severe cases, however, interruption of pregnancy may be necessary and aggressive neonatal measures may be warranted, such as cardiopulmonary ressucitation or active treatment of pulmonary hypertension with pulmonary vasodilator drugs, nitric oxide or high-frequency ventilation. Even though the association between the duration of prenatal ductal constriction and severity of pulmonary hypertension has not yet been established, it seems logical to suppose that a shorter duration of ductal constriction could be less harmful. Thus, the ideal moment for the interruption of pregnancy will take into account fetal pulmonary maturation, severity of the manifestations of ductal constriction and the presence of progressive hemodynamic changes during evolution.

In the immediate neonatal period, the fall in pulmonary vascular resistance associated with physiological closure of the ductus allows normalization of cardiocirculatory alterations secondary to right ventricular afterload increase. However, as already mentioned, a prolonged increase in fetal right ventricular pressure may prompt a neonatal reactive pulmonary arteriolar vasoconstriction, with a consequent pulmonary arterial hypertension, which will need intensive treatment.

Persistent pulmonary hypertension of the newborn without any known cardiac abnormalities occurs in one out of 1000 liveborns and approximately 23% of these do not have a detectable etiology. It is speculated that many of these cases could be secondary to constriction of the ductus arteriosus not diagnosed during fetal life [33].

Anti-inflammatory activity of polyphenol-rich substances

In recent years, many investigations have tried to demonstrate the actual therapeutic effect of substances present in nature and classically used by the general population. Several of these

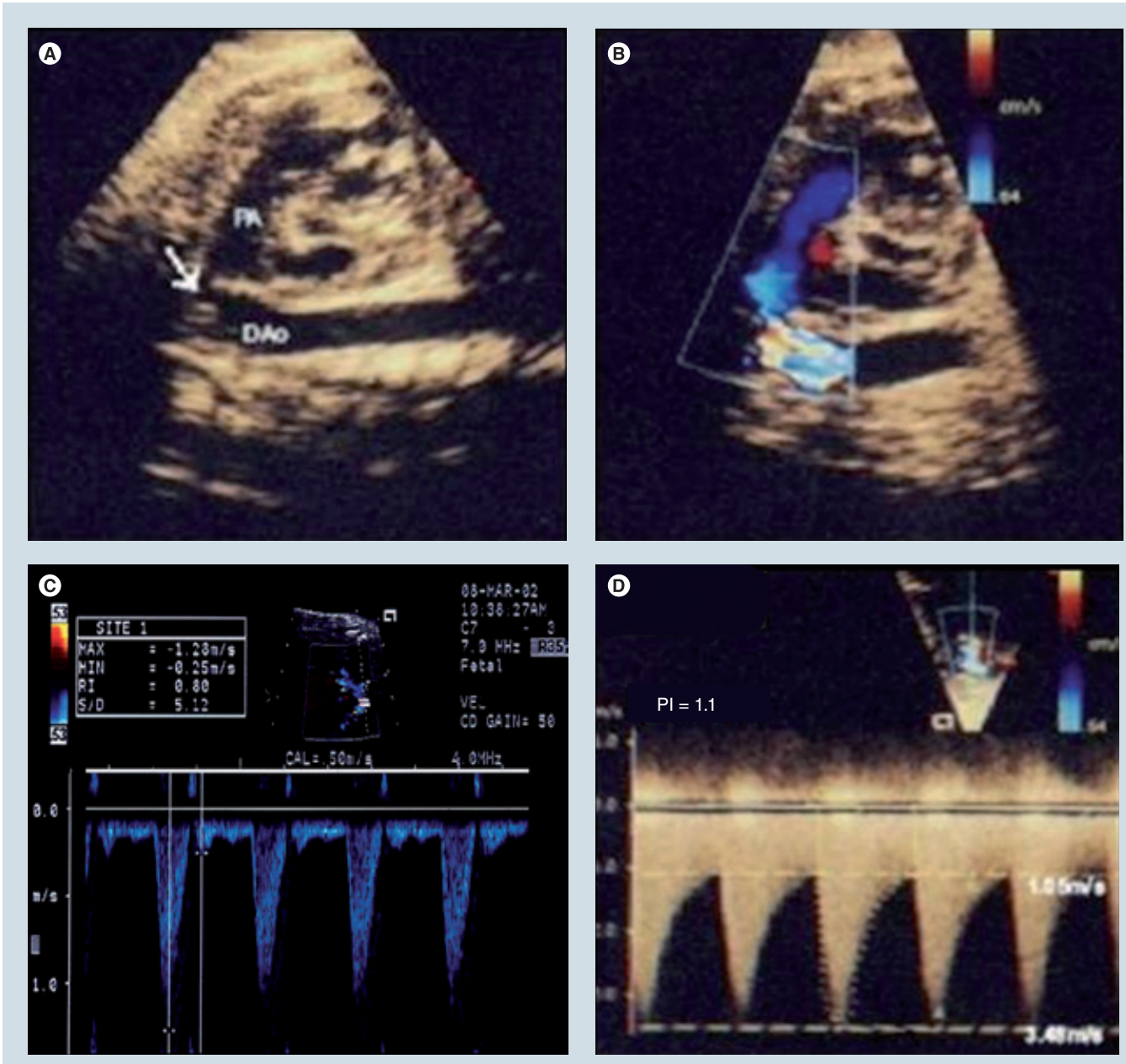

Figure 1. Doppler echocardiographic diagnosis of fetal ductal constriction. (A) Sagital view of the ductal arch, with a severe narrowing of the ductus (arrow). **(B)** Color-flow mapping showing a turbulent flow at the site of ductal constriction. **(C)** Normal ductal flow Doppler tracing. **(D)** Doppler tracing of ductal flow with high systolic and diastolic velocities and a low pulsatility index in a fetus with ductal constriction.

substances have well-documented anti-inflammatory and anti-oxidant effects; their action upon the chain of oxidative stress production, related to inflammatory mediators such as COX-2, prostaglandin E1–2, metaloproteinase and others has also been demonstrated. Examples of these substances are foods and beverages that are rich in polyphenols or flavonoids. They are consummed worldwide, and are considered beneficial to many age groups; their daily usage is being increasingly advocated owing to their actions dependent on their antioxidant and anti-inflammatory activities.

Green tea, for example, is made up of young leaves from the plant *Camelia sinensis*. Approximately 30–40% of the leaves' solid extract is composed of polyphenols, substances with known anti-oxidant and anti-inflammatory effects, mainly catechins. Among the most important catechins present in green tea are epicatechin, gallate-3-epicatechin, epigallocatechin and, predominantly, gallate-3-epigallocatechin, with 7 g per 100 g of dry leaves. Several *in vitro* studies, in animals but also in humans, have shown its antioxidant, anticarcinogenic, anti-inflammatory, probiotic and antimicrobial actions secondary to inhibition of endogenous inflammatory

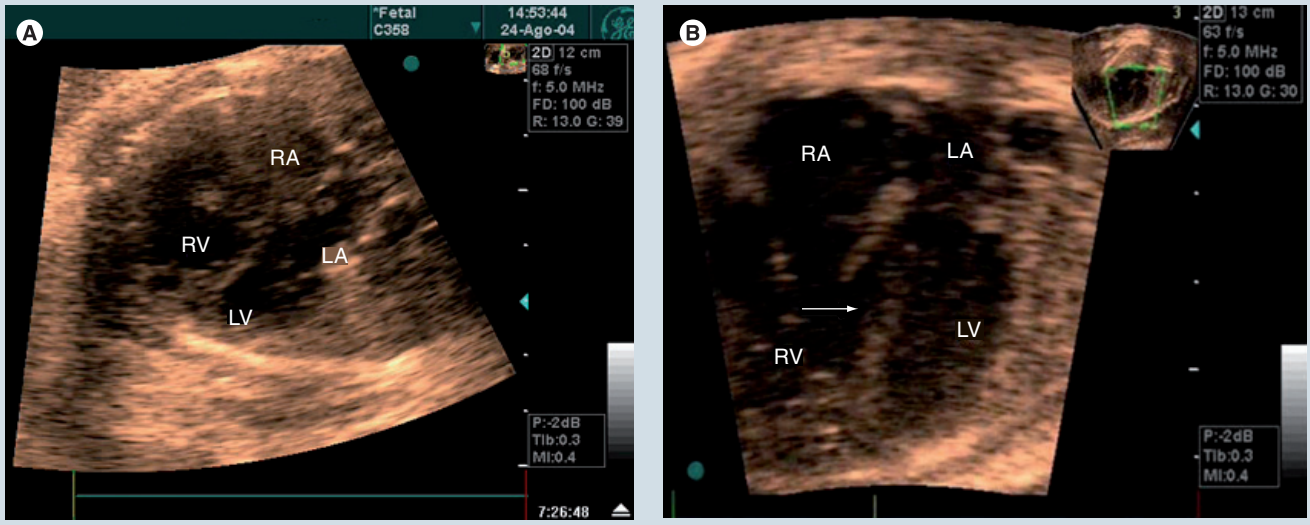

Figure 2. (A) Four-chamber view of a fetus with a normal heart. (B) Four-chamber view of a fetus with ductal constriction showing a very large right ventricle and an increased right to left ventricular dimensions ratio, with bulging of the interventricular septum from right to left.
LA: Left atrial; LV: Left ventricular; RA: Right atrial; RV: Right ventricular.

response, dependent on the interference on the prostaglandin synthesis pathway [34–37]. Black tea has also been shown to be rich in catechins, and the tea compound envolving theaflavin has been demonstrated to act on nitric oxide and on the liberation of arachdonic acid. It has also been stated that all tea drinkers could benefit from protective cardiovascular effects exerted by tea.

Resveratrol, a polyphenol compound found in grape rind, grape juice and red wine, is known by its antioxidant, antithrombotic, anti-inflammatory and anticarcinogenic actions. Several studies have demonstrated the effect of resveratrol upon the nervous system, as well as on the liver and the cardiovascular system. One of the possible mechanisms that explain its biological activities is related to a decrease in liberation of arachdonic acid, thus affecting induction of COX-2, with a consequent reduction in prostaglandin synthesis [38–40].

Mate tea, a typical regional beverage very rich in flavonoids, widely consumed in South America, mainly in Paraguay, Brazil, Argentina and Uruguay, is obtained from the dried and minced leaves of *Ilex paraguariensis*. Many studies have shown the effect of mate tea as a potent antineoplastic, anti-inflammatory and antioxidant agent, due to the action of its polyphenolic compounds [41].

Orange juice has been demonstrated to have important antioxidant activity as a result of a high content of polyphenols, especially quercitin, and the ability of the phytochemical to interact with biomembranes. It was speculated that the daily consumption of orange juice might be useful in providing additional protection against cellular oxidation *in vivo* [42].

Dark chocolate shows high concentrations of flavonoids and has anti-inflammatory properties. It has been demonstrated to have an inverse association with C-reactive protein, in amounts as low as 20 g every 3 days, suggesting that the regular ingestion of dark chocolate may reduce inflammatory processes.

Many other substances present in nature commonly used in daily routine by the general population have also shown definite anti-inflammatory effects secondary to inhibition of the prostaglandin synthesis pathway [43]. Examples are boldine [44], with anti-inflammatory and antithermic activities, propolis [45], with anti-inflammatory action in asthmatic patients, passion fruit [46], with cytotoxic, anti-inflammatory and scar-promoting effects, tomato and ginseng [47], also with anti-inflammatory action on COX-2, salvia [48], with anti-inflammatory effects on acute and chronic processes, chamomilla [49], with moderate antioxidant and antimicrobial activity and significant antiplatet actions, and many others with variable concentrations of flavonoids.

Role of a polyphenol-rich maternal diet during late pregnancy on fetal ductus arteriosus constriction

An increasing number of cases of fetal ductal constriction not associated with the consumption of nonsteroidal anti-inflammatory drugs during pregnancy have been observed [50]. We hypothesized that flavonoid or polyphenol-rich substances usually consumed by mothers in late pregnancy could influence the dynamics of fetal ductus arteriosus and could even cause ductal constriction, by inhibiting COX-2 and the prostaglandin synthesis pathway.

A cohort of 41 fetuses with gestational ages beyond 30 weeks sequentially seen from late 2005 to early 2007 with the diagnosis of ductal constriction unrelated to maternal intake of nonsteroidal anti-inflammatory drugs was analyzed. There was evidence of heavy maternal ingestion of polyphenol-rich foods (green tea, mate tea, Indian tea, boldine tea, dark chocolate, olive oil, orange juice, grape juice and others). Immediate discontinuation of these substances was recommended, and a control echocardiogram

was obtained after 1–3 weeks in 30 fetuses. Of these, 29 (96%) showed important improvement or complete recovery of the signs of ductal constriction. There was significant association between improvement and polyphenol discontinuation. At this point, we considered that these results pointed in the direction of a corroboration of our hypothesis [51].

An experimental study was then designed to test the hypothesis that a cause-and-effect relationship between maternal ingestion of polyphenol-rich substances in late pregnancy and fetal ductal constriction was present. A total of 13 near-term (>120 days) Corriedale fetal lambs were submitted to fetal Doppler echocardiography with color-flow mapping before and 1 week after maternal administration of concentrated dosages of green tea, mate tea and grape juice as the only source of liquid. In all fetuses, unequivocal Doppler echocardiographic and/or histopathological evidence of a constrictive action on the ductus arteriosus were demonstrated. A control group of four fetal lambs submitted to a habitual diet did not show significant differences in ductal velocities and right to left ventricular ratios 1 week after the first examination, and did not show any alteration in ductal histology. This experimental study provided evidence that maternal administration of the polyphenol-rich beverages green tea, mate tea and grape juice at late gestation was associated with constriction of fetal ductus arteriosus [52].

The next step was to test the hypothesis that maternal intake of polyphonol-rich substances in the third trimester of normal human fetuses interferes with ductus arteriosus dynamics. We prospectively examined 102 fetuses exposed to polyphenol-rich foods (daily estimated maternal consumption >75th percentile, or 1089 mg) compared with 41 unexposed fetuses (flavonoid ingestion <25th percentile, or 127 mg). Mean peak systolic and diastolic velocities as well as the mean right ventricular/left ventricular (RV/LV) ratio were significantly higher in the 102 exposed than in the 41 nonexposed fetuses. We concluded that ductal flow velocities are higher and the RV/LV ratio is larger in fetuses exposed to maternal ingestion of polyphenol-rich substances than in those not exposed. It seems clear that ductal flow response to the consumption of polyphenols during pregnancy is not a categorical parameter, but rather a continuous dose-dependent variable. These alterations were probably related to the anti-inflammatory effects of these substances by the inhibition of prostaglandin synthesis. Since the maternal intake of polyphenol-rich foods in late gestation may trigger alterations in fetal ductal dynamics, changes in perinatal dietary orientation are warranted [53].

A clinical cohort still under evaluation in an open clinical trial, in order to assess the role of the dietary intervention in fetal ductal dynamics, is composed of third-trimester normal pregnancies with normal fetuses submitted to nutritional intervention at the second visit, 2 weeks after a first echocardiographic examination in which no intervention is made. Following another 2 weeks after the introduction of a maternal diet poor in polyphenol substances, a third fetal echocardiogram is performed. Partial results at this time, based on the first 46 fetuses studied, confirm the conceptual hypothesis that there are no differences in fetal ductal flow velocities and in RV/LV ratios when the same amount of flavonoid substances are consumed by the mothers, while there is a significant decrease in ductal velocities and in RV/LV ratios, as well as a significant increase in pulsatility index, after a dietary intervention directed to decrease maternal ingestion of polyphenol-rich foods is performed [Zielinsky P *et al.*, Unpublished Data].

The amount of flavonoids necessary to trigger clinically significant fetal ductal constriction and the role of other substances rich in flavonoids consumed during gestation in fetal ductal flow dynamics are now being investigated in our unit, both clinically and experimentally.

Expert commentary

Fetal ductus arteriosus constriction is a frequent clinical situation in fetal cardiology, easily detectable by fetal echocardiography, especially in the third trimester. As a result of an increased right ventricular pressure, which may present with tricuspid regurgitation and even signs of heart failure, there is a risk for the development of neonatal pulmonary artery hypertension, a potentially lethal disorder. The etiology of fetal ductal constriction has long been associated with the maternal intake of nonsteroidal anti-inflammatory drugs in late pregnancy. We have shown clinical and experimental evidence that maternal consumption of polyphenol-rich substances, with antioxidant and anti-inflammatory activities dependent on inhibition of the prostaglandin synthesis pathway, may interfere with fetal ductus arteriosus dynamics and even cause ductal constriction. This knowledge should prompt discussions in order to change the dietary orientation in the third trimester of pregnancy, aiming to limit maternal ingestion of foods with higher concentrations of polyphenol-rich substances to prevent premature fetal ductal constriction.

Five-year view

Diagnosis of ductus arteriosus constriction during fetal life is straightforward, but its etiology and management have been based almost exclusively on the knowledge that anti-inflammatory drugs that interfere with the prostaglandin synthesis may trigger its appearance. Maternal administration of phosphodiesterase inhibitors have been proposed as a possible therapeutic action, but it has been tested only experimentally in rats. The hypothesis that other substances widely used by pregnant women in the routine daily diet could have the same effect, secondary to the same mechanism, such as polyphenol-rich foods, represents a new view of this important clinical situation, and is being tested by clinical and experimental studies.

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Key issues

- Fetal constriction of the ductus arteriosus in the third trimester of pregnancy is a very frequent and often underdiagnosed clinical situation.
- Ductal constriction during fetal life is a definitive risk factor for neonatal pulmonary hypertension.
- The well-known role of maternal intake of nonsteroidal anti-inflammatory drugs in the etiology of fetal ductal constriction is important, but is observed in less than one third of cases.
- Maternal ingestion of polyphenol-rich foods, such as herbal teas, grape juice, orange juice, dark chocolate and many others, in late pregnancy has been shown to interfere with the dynamics of fetal ductus arteriosus, as a result of inhibition of the prostaglandin synthesis pathway, which may result in ductal constriction with variable hemodynamic significance.

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•• **Shows for the first time that th maternal consumption of polyphenol-rich foods in the third trimester influences the flow pattern in fetal ductus arteriosus.**

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