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Monitoring fetal well-being in labor in late fetal growth restriction.

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Abstract

Late-onset fetal growth restriction (FGR) accounts for approximately 70–80% of all cases of FGR secondary to uteroplacental insufficiency and is associated with an increased risk of adverse antepartum and perinatal events, which in most instances result from hypoxic insults either present at the onset of labour or supervening during labour as a result of uterine contractions. Labour represents a stressful event for the fetoplacental unit being uterine contractions associated with an up-to 60% reduction of the uteroplacental perfusion. Intrapartum fetal heart rate monitoring by means of cardiotocography (CTG) currently represents the mainstay for the identification of fetal hypoxia during labour and is recommended for the fetal surveillance in the case of FGR or other conditions associated with an increased risk of hypoxia during labour. In this review we discuss the potential implications of an impaired placental function on the intrapartum adaptation to the hypoxic stress and the role of the CTG and alternative techniques for the intrapartum monitoring of the fetal wellbeing in the context of FGR secondary to uteroplacental insufficiency.

Introduction

Fetal growth restriction (FGR) is a complex and multifactorial disorder characterized by pathological smallness that is associated with an increased risk of adverse antepartum and perinatal events and represents a risk factor for long-term neurodevelopmental, metabolic and cardiovascular disorders [1-7]. Uteroplacental insufficiency, congenital infections, genetic syndromes and chromosomal abnormalities are among the potential aetiologies, the former accounting for the vast majority of FGR. The disease is subclassified into early-onset and late-onset FGR according to the gestational age at diagnosis of the disease, with an arbitrary cut-off conventionally set at 32 weeks [8]. Late-onset FGR accounts for approximately 70–80% of all cases of FGR of uteroplacental origin and differs from its early-onset counterpart in terms of clinical manifestations, frequency of associated hypertensive disorders of the pregnancy and patterns of fetal deterioration as a result of the lower extent of impaired placental function [9].

Over decades multiple definitions of FGR have been suggested [10-13]. Recently, a consensus-based definition of late-onset FGR reached though a Delphi procedure involving international Fetal Medicine experts defined late-onset FGR as either estimated fetal weight (EFW) or abdominal circumference (AC) below the 3rd centile or by the combination of at least two among AC or EFW <10^{th} centile, longitudinal reduction of the EFW or the AC growth of at least 2 quartiles on growth centiles and cerebroplacental ratio (CPR) <5^{th} centile or umbilical artery pulsatility index (PI)> 95^{th} centile [14].

According to the most recent and widely agreed definition fetal smallness is not a synonym of FGR. Indeed, also fetuses sized above the 10th centile may be growth restricted as they may have slowed their growth, hence failed to reach their growth potential. The concept that placental insufficiency may affect also fetuses weighing above the 10^{th} percentile is supported by several studies investigating the role of the Doppler indicators of cerebral redistribution in appropriately grown

fetuses demonstrating an increased risk of intrapartum fetal distress and a higher frequency of small-for-gestational age (SGA) neonates in cases showing Doppler features of fetal hypoxia [15-18]. However, if we assume that fetal smallness is related to underlying placental insufficiency, then an EFW <10th percentile has been shown to represent the best clinical surrogate of FGR in the third trimester [19].

Intrapartum fetal heart rate monitoring by means of cardiotocography (CTG) currently represents the mainstay for the identification of fetal hypoxia occurring during labour and is recommended for the fetal surveillance during labour in the case of FGR or other conditions associated with an increased risk of hypoxia potentially leading to cerebral palsy and stillbirth [20-21]. The presence of FGR needs to be considered while interpreting the CTG trace. Labour represents a stressful event for the fetoplacental unit as uterine contractions have been associated with an up-to 60% reduction of the uteroplacental perfusion. On this basis, labour may impact on the CTG findings of the fetuses with a pre-existing chronic hypoxia secondary to a reduced functional reserve of the placenta [22-25]. In this review we discuss the potential implications of an impaired placental function on the intrapartum adaptation to the hypoxic stress and the role of the CTG and of alternative techniques for the intrapartum monitoring of the fetal wellbeing in the context of FGR secondary to uteroplacental insufficiency.

Pathophysiology of placental insufficiency and adaptation in fetal growth restriction of uteroplacental origin

Placental insufficiency is associated with an intrauterine hypoxic environment which leads to the activation the mechanisms of adaptation to chronic hypoxia. These include the reduction of the consumption of oxygen and the regulation of the flow through the shunts of the fetal circulation such as the ductus venosus and arteriosus, leading to the diversion of the oxygenated blood towards the tissues at highest risk of hypoxic-related injury [26-27]. In order to maintain the oxygenation of the "central organs" – i.e. the brain and the heart – the fetus undergoes splanchnic and skin vasoconstriction, reduces the body temperature and abolishes non-essential activities such as movements and releases catecholamines, primarily adrenaline and noradrenaline. Such "basal" increase of the catecholamines activity leads to the increase of the fetal heart rate and to the so-called "brain sparing effect", which consists in the coexistence of a peripheral vasoconstriction and a cerebral vasodilatation and is responsible for the diversion of the blood flow from nonessential peripheral organs to the brain and to the heart [27]. Such redistribution of the blood flow can be documented by means of a reduced cerebroplacental ratio (CPR) or pulsatility index (PI) in the middle cerebral artery indicating low blood flow resistance in the cerebral circulation [28-29]. The adaptation of the autonomic nervous system in chronically hypoxic fetuses seems also to impact the fetal heart rate variability, as demonstrated in a longitudinal study by Shaw et al. showing that the exposure of fetal sheep to chronic hypoxia at advanced gestational age has the potential to alter the development of the autonomic control of the FHR and reduce the fetal heart rate variability [30].

Labour is a stressful event for the fetus as uterine contractions are associated with an up to 60% reduction in the utero-placental circulation, thus determining an intermittent reduction of the flow of oxygenated blood that reaches the fetus. On this ground, if we assume that FGR is secondary to

placental insufficiency leading to chronic hypoxia, the onset of labor in FGR can be seen as a superimposed hypoxic stress which has the potential to exacerbate a condition chronically hypoxiemia. Based on available evidence, the "cerebral redistribution" characterizing antepartum chronic hypoxia is present also in the case of hypoxia occurring during labour [27].

When labour hypoxic stress supervenes in a fetus with pre-existing chronic hypoxia, the fetus is required to reduce further its oxygen consumption in order to keep a positive energy balance. Available evidence suggests that the fetal exposure to chronic hypoxia before labour results in an attenuation of the defence mechanisms against hypoxic stress, which increases the susceptibility of the fetus to the hypoxic insults that may occur in labour [31-36]. On this basis, the mechanisms characterizing fetal adaptation to slowly evolving hypoxia may not follow the sequence of events which is known to occur in previously normoxemic fetuses. This can be determined by the fact that the adrenal glands are of small size in FGR fetuses, which determines a low reserve of catecholamines, furthermore the storage of glycogen in the liver and in the myocardium is reduced in FGR fetuses exposed to a chronically hypoxic environment. Other factors potentially determining the different sequence of adaptive events in FGR fetuses are represented by the limited amount of Wharton's jelly as well as the small size of the umbilical cord, which may determine a longer duration of the decelerations of the FHR by limiting the restoration of the umbilical cord blood flow following uterine contractions. Of note, it is important to point out that the fetuses exposed to long-standing hypoxia prior to labour may show a FHR pattern indicating a pre-existing injury affecting the fetal nervous system. This is featured by a static FHR which cannot be modified by intrapartum maneuvers. In such cases, the response to a "new onset" hypoxic event is characterized by decelerations that are typically shallow and low in amplitude.

Perinatal and labour complications associated with fetal growth restriction and placental insufficiency

At present no approach is available to reduce the impairment of the placental function and the only treatment option for FGR is delivery. However, available evidence has shown that the identification of fetal smallness per se is associated with improved perinatal outcomes as it allows the implementation of antenatal management strategies including the serial assessment of the fetal wellbeing and timed delivery [37].

FGR is an acknowledged risk factor for antepartum and intrapartum complications, whose incidence increased with decreasing fetal size [9][38] and is associated with an increased incidence of labour induction as well as of obstetric interventions including emergency caesarean section due to intrapartum fetal compromise [39]. In a study including 5416 apparently uncomplicated term pregnancies, Mendez- Figueroa et al [40] found an increased incidence of neonatal death in SGA neonates, while another cohort study of 115,502 uncomplicated singleton term pregnancies showed an association between the postnatal diagnosis of SGA and composite hypoxic neonatal morbidity [41], whose risk was 40% higher in SGA compared to normally grown neonates. Consistently, a large case-control study including 493 babies born >35 weeks and subsequently diagnosed with cerebral palsy found that severe smallness – as defined by birthweight below 2 standard deviations for the given gestation – is associated with an almost five-fold higher risk of cerebral palsy.

Consistently with the most recent and widely agreed definition of FGR, which supports the concept that also fetuses with an EFW> 10th centile may show the features of placental insufficiency, several observational studies have demonstrated an increased rate of adverse perinatal outcomes including NICU admission and perinatal death in appropriate-for-gestational age (AGA) fetuses not fulfilling the criteria for FGR but showing decelerating growth [42] or cerebral redistribution at or close to

delivery [18]. Such largely undetected subgroup of fetuses affected by subclinical placental insufficiency is likely to be accounted for the vast majority of the cases of stillbirth occurring in the third trimester and of adverse labor events recorded in AGA fetuses [37][43].

CTG features of the growth restricted fetus

The use of continuous intrapartum electronic fetal heart rate monitoring (EFM) by means of cardiotocography (CTG) has been introduced in the clinical practice developed with the aim to identify fetal hypoxia and prevent asphyxia, thus improving perinatal outcomes [44]. Following its implementation, CTG has been shown to yield a good sensitivity but a low positive predictive value for intrapartum hypoxia, being its overall specificity as low as 30% [44], and available evidence has shown that the routine use of intrapartum CTG is associated with increased rates of obstetric interventions not accompanied by a decreased frequency of death, cerebral palsy and other labor complications [45].

Fetal growth restriction is among the acknowledged risk factors for intrapartum hypoxia and is currently among the indications for continuous CTG monitoring during labor [20-21], however to date no evidence supports its role in improving labor outcomes of growth restricted fetuses.

While the characteristics of the normal CTG are acknowledged and listed in the existing classification systems [20], the "baseline" CTG features of growth restricted fetuses may differ from those of appropriately grown fetuses. Placental insufficiency is known impact the CTG features primarily in terms of baseline FHR which increases in response to the catecholamines response secondary to chronic hypoxia.

Studies evaluating the CTG features of growth restricted fetuses [47-50] reported a higher proportion of "lower amplitude" accelerations and a lower number of total accelerations [48] compared to normally grown fetuses. Furthermore, a higher baseline FHR and a reduced variability have been reported in FGR compared to normally grown fetuses [49-50]. Data from a retrospective cohort of over 5000 non-anomalous term gestations investigating the CTG pattern during the second stage of labour demonstrated an increased frequency of decelerations and a lower rate of accelerations and fetal tachycardia in FGR compared to AGA fetuses during the 30 minutes prior to

delivery, with no difference in the FHR variability [47]. Consistently, a randomized controlled trial by Chauhan et al. found a reduced frequency of accelerations during the last hour of labor in growth restricted compare to normally grown fetuses. Furthermore, the rate of variable decelerations lasting greater than 60 seconds with depth greater than 60 beats per minute (bpm) or nadir less than 60 bpm were significantly more common in FGR fetuses, with no difference in terms of frequency of late and prolonged decelerations and fetal bradycardia. Of note, the trial could not demonstrate any difference in the rate of neonatal morbidity between FGR and AGA fetuses [51].

Alternative techniques for the intrapartum monitoring of the fetal wellbeing in fetal growth restriction

Computerized CTG (cCTG) has been developed in the 1990s with the aim to improve the recognition of abnormal FHR patterns by reducing the intra- and inter-observer variability. Such automated analysis of CTG tracings can be performed by means of different algorithms [52][53] and requires the processing of the uterine contraction signals, the long- and short-term variability, the estimation of the FHR baseline, the presence accelerations and the detection and classification of decelerations. Algorithms calculate these variables based on pre-programmed system-specific criteria. While the role of cCTG in the antenatal monitoring and timing of delivery of early-onset FGR in the antepartum period is supported by grade "A" evidence [54] to date no data supports the use of cCTG for the intrapartum monitoring in the context of FGR

The use of ST-segment waveform analysis (STAN) of the fetal electrocardiogram (ECG) has been implemented to detect the hypoxia in the central organs and improve the discrimination between compensated and decompensating hypoxic stress occurring during labor. STAN analysis has been available for the intrapartum fetal monitoring since 2000, and its features and contraindications have been recently addressed in another review from our group [57]. Briefly, in the presence of an acute hypoxic stress the STAN analysis can discriminate between the fetuses who can compensate and maintain a good oxygenation of the myocardium from those where there is a switch to an anaerobic metabolism in response to the hypoxic insult, which depends on the catecholamine-mediated myocardial glycogenolysis. The use of fetal ECG analysis in labor has been restricted to monitor an apparently healthy term fetuses, as in the preterm fetus the endocardial–epicardial interphase may be underdeveloped and interfere with signal conduction leading to a decreased sensitivity of this technique in heralding fetal acidaemia. Fetal growth restriction is among the other limitations to the analysis of the ST segment of the fetal ECG as the chronically hypoxic environment

which features FGR is acknowledged to be associated with low myocardial reserves of glycogen and with the limited availability of the enzymes deputed to glycogenolysis [57-58]. Furthermore, a prerequisite for the STAN analysis is the absence of pre-existing CTG features indicating a hypoxic or a non-hypoxic injury, which include the loss of variability or cycling, an unstable or abnormal FHR baseline and prolonged decelerations. On this basis, the STAN technology is not indicated for the monitoring fetal wellbeing in FGR fetuses [57] [59].

The computerized interpretation of the FHR is another technique proposed for the intrapartum monitoring of the fetal wellbeing. Two large clinical trials have been conducted in order to evaluate the impact of such strategy on labor outcomes, and their findings have been incorporated in a recent systematic review and meta-analysis summarizing the existing evidence on the topic [60]. The INFANT trial [61] included 47062 patients having continuous electronic fetal monitoring during labor, among whom known FGR accounted for less than 4% of all cases, who were randomly assigned to decision support with the INFANT computerized interpretation system versus no decision support. Despite the large study cohort, the trial failed to demonstrate any role of the computerized CTG interpretation in improving maternal or neonatal outcomes. In another trial with a similar design over 8000 women were randomized in order to investigate the role of the Omniview SisPorto decision support software in the identification of metabolic acidosis on umbilical cord gases [62]. The Omniview SisPorto system combines the interpretation of the CTG signal and of the fetal ECG (STAN) analysis and provides color-coded visual and auditory alerts notifying the operator when the system detects an increased risk of fetal hypoxia. The results of the randomized clinical trial showed a trend towards a lower rate of fetal metabolic acidosis in the group randomized to the decision support system, with no improvement of other perinatal outcomes. Not surprisingly, a recent systematic review and meta-analysis of randomised controlled trials [60] confirmed the absence of clinical benefits in terms of metabolic acidosis and obstetric intervention in women

submitted to computerized analysis of the fetal CTG. On this ground, such approach cannot be recommended for the intrapartum monitoring of late onset FGR fetuses.

Management and intrapartum monitoring of the fetal well-being in late FGR: state of the art.

Due to the lack of interventional randomized trials evaluating the role of CTG/cCTG, Doppler or other monitoring parameters, to date there is no international consensus on the timing of delivery in late FGR [63]. Furthermore, no grade "A" evidence exists as to how to identify the optimal route of delivery in late-onset FGR. The latest guidelines of the International Society of Ultrasound in Obstetrics and Gynecology [8] recommend in favour of elective caesarean section in the case of "critical" umbilical artery Doppler findings such as absent-or-reversed end-diastolic flow, while in other circumstances vaginal delivery and induction of labor may be undertaken. In such cases individualized management in terms of timing and modality of elective delivery is advised and should be based on the ultrasound and Doppler findings together with the gestational age, parity and cervical findings. In such context, the only randomized interventional trial on FGR at or close to term so far conducted [64] demonstrated that an induction-of-labor policy is not associated with an increased frequency of adverse neonatal or neurodevelopmental outcome, furthermore induction of labor did not impact on the rates of obstetric intervention. However, more recent data suggest that a risk stratification based on the severity of the fetal smallness and on the presence or absence of maternal or fetal Doppler abnormalities allows to identify those cases where induction of labor may prevent adverse perinatal outcomes with no increase in the rate of obstetric intervention [9][65-69].

With regards to the intrapartum monitoring of FGR, no evidence supports the use of CTG nor of alternative monitoring strategies for improving the perinatal outcomes in pregnancies complicated by FGR. However, the recently proposed pathophysiology interpretation of the FHR pattern may support in the identification of the cause underlying an unusual CTG pattern [70-71] and allow individualized management in the context of FGR.

From a pathophysiology perspective, prior to labour the baseline FHR is expected to be higher in the event of placental insufficiency as a result of the dysregulation of the autonomic nervous system which favours the sympathetic activity. In such context, it is important to bear in mind that the reduced dimensions of the adrenal glands together with the dysregulation of the autonomic nervous system in FGR fetuses may impact on the adaptive mechanisms including the increase of the baseline FHR in the event of acute hypoxic events supervening during labour.

The most common CTG features of growth restricted fetuses include a raised baseline which is associated with reduced FHR variability and absence of accelerations. These latter result from the reduction or the absence of fetal movements, which is a typical feature of the fetuses exposed to a hypoxic environment. In such context, the onset of uterine contractions reduces the utero-placental circulation and may precipitate the fetal provision of oxygen, with resulting hypoxemia potentially leading to hypoxia and, ultimately, hypoxic-ischaemic encephalopathy (HIE) and myocardial failure with terminal bradycardia and intrapartum stillbirth [46]. Therefore, these cases warrant careful administration of uterotonics and may benefit from the use of tocolytics and low threshold for delivery.

An abnormal CTG in early labor or prior to labor may also indicate a pre-existing injury of the fetal central nervous system which is not related to the hypoxic stress of labor. In such cases, the CTG pattern is featured by a fixed and relatively stable baseline rate, with reduced variability that does not exhibit fetal cycling and shallow decelerations. Tachycardia may occur, and is usually more marked the more recent the central nervous system insult, while a normal baseline of the FHR is more common the more remote from admission the central nervous system insult. Such pattern is static and cannot be modified by tocolysis or other intervention described for intrapartum resuscitation. Shallow decelerations are chemoreceptor-mediated and may not fulfil the criteria defining decelerations acknowledged by the international guidelines [23]. Phelan and Kim [72]

attempted a categorization of such nonreactive CTG traces on admission into three groups on the basis of the baseline FHR and of the FHR variability, concluding that the CTG features may correlated with the time at onset of the injury. In details, the finding of FHR tachycardia >160 bpm associated with a reduced or absent FHR variability was suggested to be related to a short time-interval between the injury and the CTG recording, while the finding of a normal baseline FHR associated with a reduced FHR variability is considered to represent a long interval between the brain injury and the CTG recording. When such CTG features last for over 50 minutes despite the adoption of maneuvers including changes of maternal position (to relieve supine hypotension), hydration, stopping of oxytocin infusion, and use of tocolytic drugs if uterine hyperstimulation is suspected – in order to improve uteroplacental circulation and ensure adequate delivery of oxygen to the fetus – delivery by caesarean section is warranted in order to prevent further damage to the fetus [23].

In the third case scenario, which may occur in "known" FGR fetuses or in FGR fetuses misdiagnosed at third trimester screening of the fetal growth or in normally sized fetuses with subclinical placental insufficiency, the CTG pattern is normal at the onset of labor and the consequences of the impaired placental function may manifest with increasing uterine contractions. In such cases, the CTG abnormalities most commonly mimic those characterizing gradually evolving hypoxia – i.e. repetitive decelerations associated with loss of accelerations followed by increase of the baseline FHR and loss of cycling and variability [73]– however it has to be acknowledged that in such cases the sympathetic response may be dysregulated. This may determine the limited or no increase of the baseline FHR and the altered cardiovascular response to sudden hypotensive stress, which ultimately increases the susceptibility of the fetus to the hypoxic insults that may occur in labour. In such context, the systematic adoption of a policy of low-threshold for intervention may contribute in optimizing the labour outcome of growth restricted fetuses [23,31-32].

Authors' contribution section

Andrea Dall'Asta – Conceptualization, literature review, manuscript writing and editing.

Greta Cagninelli – Literature review, manuscript writing and editing.

Letizia Galli – Literature review, manuscript writing and editing.

Tiziana Frusca – Conceptualization, manuscript review.

Tullio Ghi – Conceptualization, manuscript review.

All authors read and approved the final version of the manuscript.

References

[1] Damodaram M, Story L, Kulinskaya E, Rutherford M, Kumar S. “Early adverse perinatal complications in preterm growth-restrcited fetuses” *Aust N Z J Obstet Gynaecol.* 2011;51:204–9.

[2] Mcintire DD, Bloom SL, Casey BM, Leveno KJ. “Birth weight in relation to morbildity and mortality among newborn infants” *N Engl J Med*. 1999; 340:1234–8.

[3] Jones RA, Robertson NR. “Problems of the small for dates baby” *Clin Obstet Gynaecol*. 1984;11:499–524.

[4] Yanney M, Marlow N. “Paediatric consequences of fetal growth restriction” *Semin Fetal Neonatal Med.* 2004;9:411–8.

[5] Walker DM, Marlow N. “Neurocognitive outcome following fetal growth restriction” *Arch Dis Child Fetal Neonatal Ed.* 2008;93:322–5.

[6] Barker DJ, Osmond C, Golding J, Kuh D, Wadsworth ME. “Growth in utero, blood pressure in childhood and adult life, and mortality from cardiovascular disease” *BMJ.* 1989;298:564–7.

[7] Newsome CA, Shiell AW, Fall CH, Phillips DI, Shier R, Law CM. “Is birth weight related to later glucose and insulin metabolism? A systematic review” *Diabet Med* 2003;20:339-48.

[8] Lees CC, Stampalija T, Baschat AA, da Silva Costa F, Ferrazzi E, Figueras F, et al. “ISUOG Practice Guidelines: diagnosis and management of small-for-gestational-age fetus and fetal growth restriction” *Ultrasound Obstet Gynecol* 2020; 56: 298–312.

[9] Figueras F, Caradeux J, Crispi F, Eixarch E, Peguero A, Gratacos E. “Diagnosis and surveillance of late-onset fetal growth restriction” *Am J Obstet Gynecol.* 2018 Feb;218(2S) : S790-S802.e1.

[10] American College of Obstetricians and Gynecologists. “ACOG Practice bulletin no. 134: fetal growth restriction” *Obstet Gynecol.* 2013;121:1122–33.

[11] RCOG Green Top Guidline No.31. “The Investigation and Management of the Small-for-Gestational Age Fetus” January 2014.

[12] Lees C, Marlow N, Arabin B, Bilardo CM, Brezinka C, Derks JB, et al. TRUFFLE GROUP. "Perinatal morbidity and mortality in early-onset fetal growth restriction: cohort outcomes of the trial of randomized umbilical and fetal flow in Europe (TRUFFLE)" *Ultrasound Obstet Gynecol*. 2013;42:400–8.

[13] Dall'Asta A, Brunelli V, Prefumo F, Frusca T, Lees CC. "Early onset fetal growth restriction" *Matern Health Neonatol Perinatol.* 2017 Jan 18;3:2.

[14] Gordijn SJ, Beune IM, Thilaganathan B, Papageorghiou A, Baschat AA, Baker PN, et al. "Consensus definition of fetal growth restriction: a Delphi procedure" *Ultrasound Obstet Gynecol*. 2016;48(3):333–9.

[15] Prior T, Mullins E, Bennett P, Kumar S. "Prediction of intrapartum fetal compromise using the cerebroumbilical ratio: a prospective observational study" *Am J Obstet Gynecol*. 2013 Feb;208(2):124.e1-6.

[16] Khalil A, Thilaganathan B. "Role of uteroplacental and fetal Doppler in identifying fetal growth restriction at term" *Best Pract Res Clin Obstet Gynaecol.* 2017 Jan;38:38-47.

[17] Dall'Asta A, Ghi T, Rizzo G, Cancemi A, Aloisio F, Arduini D, et al. "Cerebroplacental ratio assessment in early labor in uncomplicated term pregnancy and prediction of adverse perinatal outcome: prospective multicenter study" *Ultrasound Obstet Gynecol*. 2019 Apr;53(4):481-487.

[18] Kumar S, Figueras F, Ganzevoort W, Turner J, McCowan L. "Using cerebroplacental ratio in non-SGA fetuses to predict adverse perinatal outcome: caution is required" *Ultrasound Obstet Gynecol*. 2018 Oct;52(4):427-429.

[19] Miranda J, Rodriguez-Lopez M, Triunfo S, Sairanen M, Kouru H, Parra-Saavedra M, et al. "Prediction of fetal growth restriction using estimated fetal weight vs a combined screening model in the third trimester" *Ultrasound Obstet Gynecol*. 2017 Nov;50(5):603-611.

[20] Ayres-De-Campos D, Spong CY, Chandraharan E. "Erratum: FIGO consensus guidelines on intrapartum fetal monitoring: Cardiotocography (International Journal of Gynecology and Obstetrics 131 (2015) (13-24)," *Int. J. Gynecol. Obstet.*, vol. 133, no. 1, p. 130, 2016.

[21] SIGO Recommendations "monitoraggio cardiotocografico in travaglio" 2018 available from https://www.sigo.it/linee-guida/sigo

[22] Chandraharan E, Perez-Bonfils AG. "Fetal Oxygenation" In E. Chandraharan (Ed.), Handbook of CTG Interpretation: From Patterns to Physiology. Cambridge: Cambridge University Press, 2017.

[23] Ghi T, Fieni S, Chandraharan E, Frusca T. "Cardiotocografia Intrapartum Concetti chiave per una nuova interpretazione" Cento (FE): Editeam 2018.

[24] Barcroft J. "The Croonian lecture: foetal respiration" *Proc R Soc Lond* 1935, B 118, 242–263,

[25] Rudolph AM, Heymann MA, "The fetal circulation" *Annu Rev Med* 1968, 19, 195–206.

[26] Maurer HS, Behrman RE, Honig GR. "Dependence of the oxygen affinity of blood on the presence of foetal or adult haemoglobin" *Nature* 1970. 227, 388–390.

[27] Giussani DA. "The fetal brain sparing response to hypoxia: physiological mechanisms" *J Physiol.* 2016 Mar 1;594(5):1215-30.

[28] Gramellini D, Folli MC, Raboni S, Vadora E, Merialdi A. "Cerebral-umbilical Doppler ratio as a predictor of adverse perinatal outcome" *Obstet Gynecol* 1992;79:416–420.

[29] Wladimiroff JW, Tonge HM, Stewart PA. "Doppler ultrasound assessment of cerebral blood flow in the human fetus" *Br J Obstet Gynaecol* 1986;93:471–475.

[30] Shaw CJ, Allison BJ, Itani N, Botting KJ, Niu Y, Lees CC, et al. "Altered autonomic control of heart rate variability in the chronically hypoxic fetus" *J Physiol.* 2018 Dec;596(23):6105-6119.

[31] Allison BJ, Brain KL, Niu Y, Kane AD, Herrera EA, Thakor AS, et al. "Altered Cardiovascular Defense to Hypotensive Stress in the Chronically Hypoxic Fetus" *Hypertension* 2020 Oct;76(4):1195-1207.

[32] Gardner DS, Fowden AL, Giussani DA. "Adverse intrauterine conditions diminish the fetal defense against acute hypoxia by increasing nitric oxide activity" *Circulation.* 2002 Oct 22;106(17):2278-83.

[33] Anderson PA, Glick KL, Killam AP, Mainwaring RD. "The effect of heart rate on in utero left ventricular output in the fetal sheep" *J Physiol* 1986. 372, 557–573.

[34] Gardner DS, Giussani DA & Fowden AL. "Hindlimb glucose and lactate metabolism during umbilical cord compression and acute hypoxaemia in the late-gestation ovine fetus" *Am J Physiol Regul Integr Comp Physiol* 2003. 284, 954–964.

[35] Browne VA, Stiffel VM, Pearce WJ, Longo LD, Gilbert RD. "Cardiac beta-adrenergic receptor function in fetal sheep exposed to long-term high-altitude hypoxemia" *Am J Physiol.* 1997;273:R2022–R2031.

[36] Zhang L, Hu X, Longo LD. "Effect of chronic hypoxia on adrenoceptor responses of ovine foetal umbilical vessels" *Br J Pharmacol.* 1998;125:136–142.

[37] Gardosi J, Madurasinghe V, Williams M, Malik A, Francis A. "Maternal and fetal risk factors for stillbirth: population based study" *BMJ.* 2013 Jan 24;346:f108.

[38] Figueras F, Gardosi J. "Intrauterine growth restriction: new concepts in antenatal surveil- lance, diagnosis, and management" *Am J Obstet Gynecol* 2011;204:288-300.

[39] Ohel G, Ruach M. "Perinatal outcome of idiopathic small for gestational age pregnancies at term: the effect of antenatal diagnosis" *Int J Gynaecol Obstet*. 1996 Oct;55(1):29-32.

[40] Mendez-Figueroa H, Truong VT, Pedroza C, Khan AM, Chauhan SP. "Small-for-gestational- age infants among uncomplicated pregnancies at term: a secondary analysis of 9 Maternal-Fetal Medicine Units Network studies" *Am J Obstet Gynecol* 2016;215:628.e1-7.

[41] Chauhan SP, Rice MM, Grobman WA, Bailit J, Reddy UM, Wapner RJ, et al. "Neonatal morbidity of small- and large-for- gestational-age neonates born at term in uncomplicated pregnancies" *Obstet Gynecol* 2017;130:511-9.

[42] Chatzakis C, Papaioannou GK, Eleftheriades M, Makrydimas G, Dinas K, Sotiriadis A. "Perinatal outcome of appropriate-weight fetuses with decelerating growth" *J Matern Fetal Neonatal Med*. 2019 Nov 13:1-8.

[43] Akolekar R, Syngelaki A, Gallo DM, Poon LC, Nicolaides KH. "Umbilical and fetal middle cerebral artery Doppler at 35-37 weeks' gestation in the prediction of adverse perinatal outcome" *Ultrasound Obstet Gynecol.* 2015; 46(1):82–92.

[44] Pinas A, Chandraharan E. "Continuous cardiotocography during labour: Analysis, classification and management" *Best Pract Res Clin Obstet Gynaecol*. 2016 Jan;30:33-47.

[45] Clarke S, Hankins G. "Temporal and demographic trends in cerebral palsy -Fact and fiction" *Am J Obstet Gynecol* 2003 Mar; 188(3):628e33.

[46] Pereira S, Chandraharan E. "Recognition of chronic hypoxia and pre-existing foetal injury on the cardiotocograph (CTG): Urgent need to think beyond the guidelines" *Porto Biomed J.* 2017 Jul-Aug;2(4):124-129.

[47] Epplin KA, Tuuli MG, Odibo AO, Roehl KA, Macones GA, Cahill AG. "Effect of Growth Restriction on Fetal Heart Rate Patterns in the Second Stage of Labor" *Am J Perinatol.* 2015 Jul;32(9):873-8.

[48] Gagnon R, Hunse C, Bocking AD. "Fetal heart rate patterns in the small-for-gestational-age human fetus" *Am J Obstet Gynecol* 1989; 161(3):779–784

[49] Henson G, Dawes GS, Redman CW. "Characterization of the reduced heart rate variation in growth-retarded fetuses" *Br J Obstet Gynaecol* 1984;91(8):751–755

[50] Nijhuis IJ, ten Hof J, Mulder EJ, Nijhuis JG, Narayan H, Taylor DJ, et al. "Fetal heart rate in relation to its variation in normal and growth retarded fetuses" *Eur J Obstet Gynecol Reprod Biol* 2000;89(1):27–33

[51] Chauhan SP, Weiner SJ, Saade GR, Belfort MA, Reddy UM, Thorp JM Jr, et al. "Intrapartum Fetal Heart Rate Tracing Among Small-for-Gestational Age Compared with Appropriate-for-Gestational-Age Neonates" *Obstet Gynecol.* 2018 Oct;132(4):1019-1025.

[52] Pardey J, Moulden M, Redman CW. "A computer system for the numerical analysis of nonstress tests" *Am J Obstet Gynecol.* 2002;186:1095–103.

[53] Kouskouti C, Jonas H, Regner K, Ruisinger P, Knabl J, Kainer F. "Validation of a new algorithm for the short-term variation of the fetal heart rate: an antepartum prospective study" *J Perinat Med*. 2018 Aug 28;46(6):599-604.

[54] Bilardo CM, Hecher K, Visser GHA, Papageorghiou AT, Marlow N, Thilaganathan B, et al TRUFFLE GROUP. "Severe fetal growth restriction at 26-32 weeks: key messages from the TRUFFLE study" *Ultrasound Obstet Gynecol.* 2017 Sep;50(3):285-290.

[55] Keith RDF, Beckley S, Garibaldi JM, Westgate JA, Ifeachor EC, Greene KR. "A multicenter comparative study of 17 experts and an intelligent computer system for managing labour using the cardiotocogram" *Br J Obstet Gynaecol* 1995;102:688–700.

[56] Grivell RM, Alfirevic Z, Gyte GM, Devane D. "Antenatal cardiotocography for fetal assessment" *Cochrane Database Syst Rev*. 2015 Sep 12;2015(9):CD007863.

[57] Cagninelli G, Dall'Asta A, Di Pasquo E, Morganelli G, Degennaro VA, Fieni S, et al. "STAN: a reappraisal of its clinical usefulness" *Minerva Ginecol.* 2020 Nov 30. [Epub ahead of print].

[58] Rosen KG, Martendal A, *The Green Book of Neoventa Part I- The physiology of fetal surveillance*. Neoventa Medical AB, 2014.

[59] Amer-Wahlin I, Arulkumaran S, Hagberg H, Maršál K, Visser GHA, "Fetal electrocardiogram: ST waveform analysis in intrapartum surveillance," *BJOG An Int. J. Obstet. Gynaecol.* 2007, vol. 114, no. 10, pp. 1191–1193,.

[60] Campanile M, D'Alessandro P, Della Corte L, Saccone G, Tagliaferri S, Arduino B, et al. "Intrapartum cardiotocography with and without computer analysis: a systematic review and meta-analysis of randomized controlled trials" *J Matern Fetal Neonatal Med.* 2020 Jul;33(13):2284-2290.

[61] INFANT Collaborative Group. "Computerised interpretation of fetal heart rate during labour (INFANT): a randomised controlled trial" *Lancet* 2017 Apr 29;389(10080):1719-1729.

[62] Costa A, Santos C, Ayres-de-Campos D, Costa C, Bernardes J. "Access to computerised analysis of intrapartum cardiotocographs improves clinicians' prediction of newborn umbilical artery blood pH" *BJOG.* 2010 Sep;117(10):1288-93.

[63] McCowan LM, Figueras F, Anderson NH. "Evidence-based national guidelines for the management of suspected fetal growth restriction: comparison, consensus, and controversy" *Am J Obstet Gynecol* 2018; 218: S855–868.

[64] Boers KE, Vijgen SM, Bijlenga D, van der Post JA, Bekedam DJ, Kwee A, et al; DIGITAT study group. "Induction versus expectant monitoring for intrauterine growth restriction at term: randomised equivalence trial (DIGITAT)" *BMJ* 2010; 341: c7087.

[65] Vollgraff Heidweiller-Schreurs CA, De Boer MA, Heymans MW, Schoonmade LJ, Bossuyt PMM, Mol BWJ, et al. "Prognostic accuracy of cerebroplacental ratio and middle cerebral artery Doppler

for adverse perinatal outcome: systematic review and meta-analysis" *Ultrasound Obstet Gynecol* 2018; 51: 313 – 322.

[66] Meher S, Hernandez-Andrade E, Basheer SN, Lees C. "Impact of cerebral redistribution on neurodevelopmental outcome in small-for-gestational-age or growth-restricted babies: a systematic review" *Ultrasound Obstet Gynecol* 2015; 46: 398–404.

[67] Hernandez-Andrade E, Stampalija T, Figueras F. "Cerebral blood flow studies in the diagnosis and management of intrauterine growth restriction" *Curr Opin Obstet Gynecol* 2013; 25: 138–144.

[68] DeVore GR. "The importance of the cerebroplacental ratio in the evaluation of fetal well-being in SGA and AGA fetuses" *Am J Obstet Gynecol* 2015; 213: 5–15.

[69] Habek D, Salihagić A, Jugović D, Herman R. "Doppler cerebro-umbilical ratio and fetal biophysical profile in the assessment of peripartal cardiotocography in growth-retarded fetuses" *Fetal Diagn Ther* 2007; 22: 452 – 456.

[70] Galli L, Dall'Asta A, Whelehan V, Archer A, Chandraharan E. "Intrapartum cardiotocography patterns observed in suspected clinical and subclinical chorioamnionitis in term fetuses" *J Obstet Gynaecol Res.* 2019 Dec;45(12):2343-2350.

[71] Ghi T, Di Pasquo E, Dall'Asta A, Commare A, Melandri E, Casciaro A, et al. "Intrapartum fetal heart rate between 150 and 160 bpm at or after 40 weeks and labor outcome" *Acta Obstet Gynecol Scand*. 2020 Oct 13 [Epub ahead of print].

[72] Phelan JP, Kim JO. "Fetal heart rate observations in the brain-damaged infant" *Semin Perinatol*. 2000;24:221–9.

[73] Ugwumadu A. "Recognition of Chronic Hypoxia and the Preterminal Cardiotocograph" In E. Chandraharan (Ed.), Handbook of CTG Interpretation: From Patterns to Physiology. Cambridge: Cambridge University Press, 2017.