

New Markers for Placental Dysfunction at Term – Potential for More

Neue Marker der placentaren Dysfunktion am Entbindungstermin – Potenzial für mehr



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ABSTRACT

The remaining placental reserve capacity at term plays a decisive role in the perinatal morbidity of mother and child. Considering advances made in the field of fetal monitoring, the routine examination methods currently used at term or late term may be insufficient to detect subclinical placental dysfunction (PD). The aim of this study is to offer an up-to-date, narrative review of the literature in the context of detecting PD at term using complementary ultrasound markers and biomarkers. Parameters of fetomaternal Doppler ultrasound and fetal cardiac function, as well as (anti-)angiogenic factors in maternal serum are potential PD markers. These may help identify patients that may benefit from an elective, early induction of labor at term, thereby potentially reducing morbidity and mortality. However, their value in terms of the optimal date of delivery must first be determined in randomized controlled trials on a large number of cases.

ZUSAMMENFASSUNG

Die verbleibende placentare Reserve am Entbindungstermin ist entscheidend für die perinatale Morbidität von Kind und Mutter. Angesichts des Fortschritts im Bereich der fetalen Überwachung sind die bislang routinemäßig eingesetzten Untersuchungstechniken am Termin bzw. in der Terminüberschreitung womöglich unzureichend, wenn es um die Detektion der subklinischen placentaren Dysfunktion (PD) geht. Ziel dieser Arbeit ist es, eine aktuelle, narrative Literaturübersicht im Kontext der PD-Detektion am Termin mittels komplementärer US- bzw. Biomarker zu geben. Zu den potenziellen PD-Markern zählen Parameter der fetomaternalen Doppler-Sonografie bzw. fetalen kardialen Funktion sowie (anti-)angiogene Faktoren im Serum der Mutter. Diese könnten eine Rolle spielen, wenn es um die verbesserte Selektion derjenigen Patientinnen geht, bei denen eine elektive, frühzeitige Geburtseinleitung am Entbindungstermin womöglich zur Reduktion der perinatalen Morbidität und Mortalität führt. Ihren Stellenwert bezogen auf die Frage des idealen Entbindungszeitpunkts gilt es jedoch vorerst in randomisiert-kontrollierten Studien mit großer Fallzahl zu klären.

Induction of Labor

More than one third of all pregnant women in Germany give birth after their estimated delivery date [1]. The placental reserve capacity determines whether the supply of the fetus at term is adequate. Placental dysfunction (PD) is often the cause of intrauterine fetal death (IUFD) as well as intrapartum fetal hypoxia, which is associated with serious complications such as asphyxia and hypoxic encephalopathy [2]. The uterine contractions that occur during labor and the subsequent compression of the uterine blood vessels physiologically reduces the uteroplacental perfusion by up to 60% [3]. Hence, the prenatal placental function is pivotal when it comes to the adequate fetal response to this natural stress situation. In other words: PD increases the risk of neonatal (5-min Apgar < 7, low umbilical cord arterial pH) and maternal (surgical delivery due to fetal distress, as shown by a pathological CTG or pathological fetal blood analysis) morbidity.

In some pregnancies at term, intrapartum hypoxia may result as a consequence of unforeseeable acute events such as uterine rupture, umbilical cord prolapse or placental abruption. However, most cases occur due to the gradual decline of the fetus' ability to tolerate the delivery process [4]. Up to 60% of fetuses that develop an oxygen deficiency during labor did not exhibit any prior apparent prenatal risk factors [5]. It is likely that in these pregnancies, a subclinical PD is present before the onset of uterine contractions, even though the underlying processes are not yet fully understood [4].

In light of the technical advances in the field of fetal monitoring, the routine examination methods currently used at term and the "classic" PD markers such as amniotic fluid volume, estimated fetal weight (EFW) and fetal heart rate patterns (FHR) may be insufficient to adequately assess placental function. While an oligohydramnios (single deepest pocket < 2 cm [6]), a low estimated fetal weight (EFW) and an abdominal circumference (AC) between the 3rd and 10th percentile (SGA: small for gestational age [7]) or below the 3rd percentile (FGR: fetal growth restriction [7]), as well as pathological changes of the fetal heart rate patterns (according to FIGO [8, 9]) are all pivotal for the diagnosis of a PD, the concentration on solely these parameters bears the risk of overlooking an inapparent PD which may potentially effect perinatal outcome. In addition to this, there are theoretical limitations in the pathophysiological climax of the PD (oligohydramnios – due to insufficient fetal renal circulation – as a typical late sign of PD) [10, 11], technical limitations due to the limited reproducibility and predictive power of cardiotocography (CTG) [8, 12–14] as well as – with regard to the EFW – a reinterpretation of FGR independent of cut-off values (meaning, a FGR and thus, a PD may also occur at an EFW > 10th percentile) [7] and the "ideal" birth weight percentile [15].

The aim of this study is to offer an up-to-date, narrative review of the literature in the context of detecting PD at term using complementary markers. Parameters of fetomaternal Doppler ultrasound and fetal cardiac function as well as (anti-)angiogenic factors in maternal serum are potential PD markers. These parameters should be assessed based on the added diagnostic and predictive value they provide, particularly in relation to the optimal induction of labor date for low-risk populations. In this context,

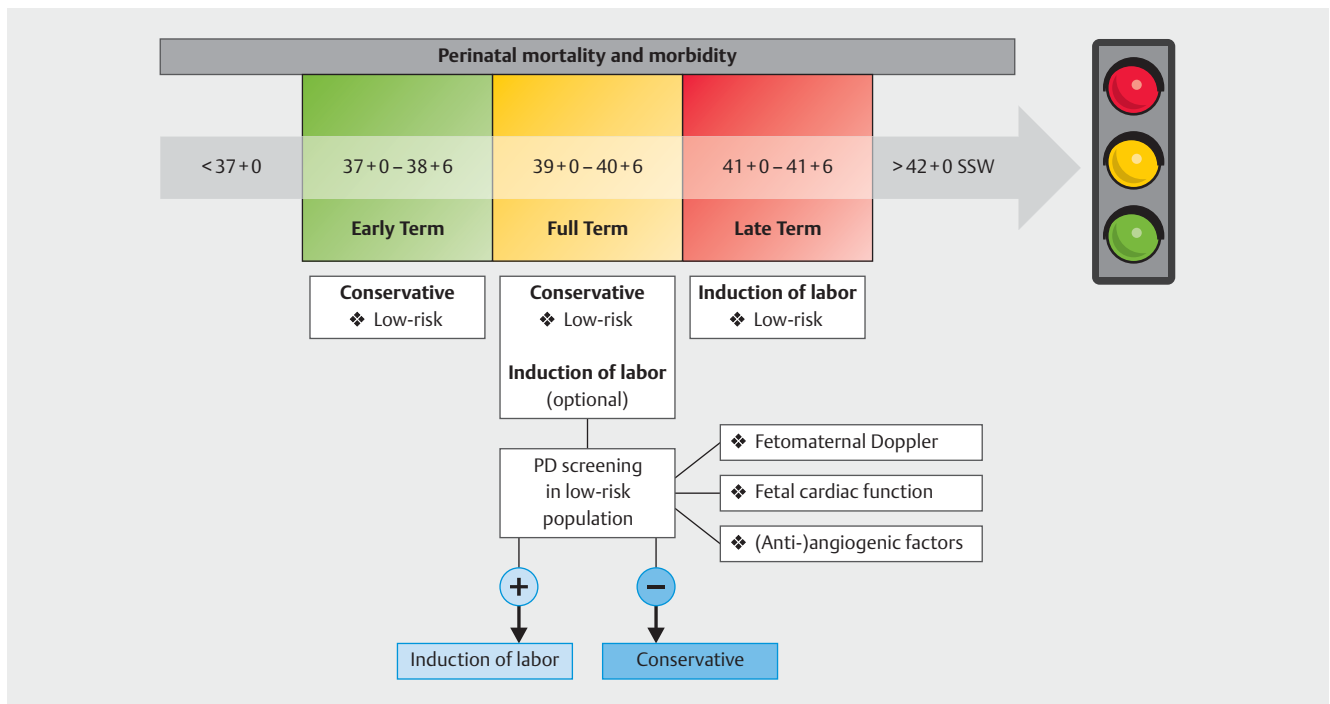
the goal is to evaluate the potential with regard to an improved selection from the collective of pregnant women at term that may benefit from an elective induction of labor through the reduction of perinatal morbidity and mortality.

Optimal Date for Induction of Labor?

The results of a large randomized controlled trial concerning the clinical benefit of induction of labor at term (ARRIVE study: A Randomized Trial of Induction Versus Expectant Management) indicate that in primipara without relevant risk factors an elective induction of labor from 39 + 0 weeks of gestation (WG) may lower the caesarean section rate without negatively influencing the perinatal outcome [16]. Furthermore, a recent study of a large number of cases (n = 53 843) was able to demonstrate that the elective induction of labor from 39 + 0 WG did not seem to have an influence on the child's school performance at an age of 8 years [17]. Recently, an increased rate of IUFD could be observed when exceeding the delivery date and prolongating beyond 41 + 0 WG (SWEPI study: SWEdish Post-term Induction Study), although methodological limitations – particularly those concerning the heterogeneity of the study population – need to be considered [18]. Moreover, a non-inferiority study published in the same year could not support these results concerning the benefit of induction of labor in 41 + 0 WG with regard to the perinatal mortality (INDEX study: Induction of labor at 41 weeks versus expectant management until 42 weeks) [19]. Based on these results, it cannot be directly concluded that exceeding the delivery date should generally be avoided and an induction of labor at 39 + 0 WG favored, in accordance with the ARRIVE study. It does, however, raise the question to what extent the "offer" of induction of labor at 41 + 0 WG, that is recommended in the national guidelines, should not only be an offer to pregnant women, but rather a medical recommendation based on these data [20]. Furthermore, a current Cochrane review on the question of induction of labor from 37 + 0 WG in a low-risk population (n = 34 randomized controlled trials of > 21 000 pregnant patients in total) showed that a significant reduction of perinatal mortality (0.4 vs. 3 deaths per 1000) can be achieved with induction of labor from 37 + 0 WG when compared to conservative management. The induced population demonstrated a lower caesarean section rate without an increase in the operative vaginal delivery rate and was also associated with fewer transfers to the neonatal intensive care unit (NICU) [21]. In contrast, however, a current epidemiological study of 39 199 viviparous children (singleton pregnancies) between 37 + 0–41 + 0 WG examined their neurocognitive development at the age of 8 months, 4 and 7 years – stratified by the WG at delivery. Here, a progress in gestational weeks up until 41 + 0 WG was associated with a significant increase in neurocognitive development scores [22].

Definition "at Term"

A temporal subdivision of "term" into early (37 + 0–38 + 6 WG), full (39 + 0–40 + 6 WG) and late term (41 + 0–41 + 6 WG), as is suggested by Spong and colleagues, seems essential considering the variations of perinatal mortality between these time periods



► **Fig. 1** Schematic depiction of the term-dependent morbidity and mortality risk (early, full and late term). A potential “term screening” (consisting of fetomaternal Doppler, fetal cardiac function, antiangiogenic factors) could aid in better assessing the APO risk of low-risk pregnant women and thus inducing labor at the right point in time.

[23]. Worth mentioning here are two significant epidemiological studies that examined perinatal mortality (pre-, intra- and post-partal) at term: Based on a population of 700 878 singleton pregnancies between 37 + 0 and 43 + 0 WG, Smith et al. observed the lowest statistical risk for perinatal death at 38 + 0 WG (1.8/1000), with a continual increase up to 41 + 0 WG (3.8/1000). Beyond that, the mortality risk for the fetus significantly increases to 5.4/1000 (42 + 0) and 9.3/1000 (43 + 0) [24]. In contrast to this, a recent meta-analysis by Muglu et al. (n = 15 000 000 pregnancies) merely observed a significant risk increase beyond 41 + 0 WG (3.18/1000). Between 37 + 0 (0.11/1000) and 41 + 0 WG, it remained constant [25].

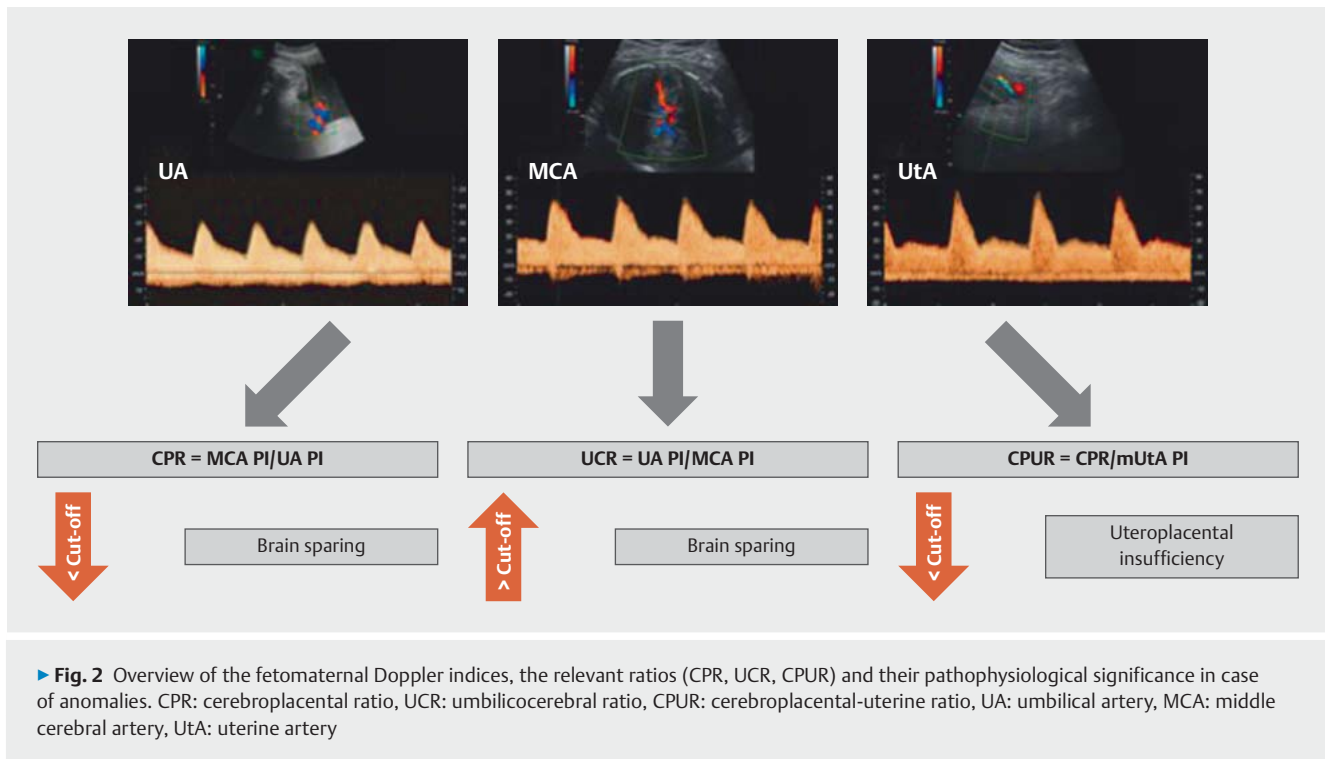
► **Fig. 1** depicts a schematic and simplified overview of the term-dependent morbidity and mortality risk (early, full and late) in the form of a traffic light. Considering the typical perinatal PD situations such as late-onset SGA/FGR, preeclampsia (PE)/hypertensive disorders of pregnancy and insulin-dependent (gestational) diabetes, the gestational age limits beyond which an induction of labor should be strived for seem evident (late-onset FGR: 37 + 0 WG, late-onset SGA: 38 + 0–40 + 0 WG, late-onset PE: 37 + 0 WG, iGDM: 40 + 0 WG) [20]. In the high-risk population, the sensitive phase of late term (“red traffic light”) – with regard to perinatal morbidity and mortality – is either naturally not reached or the gestational age limit not surpassed.

But what about the low-risk pregnant women that may have a PD independent of EFW, CTG and amniotic fluid volume? Based on current information, a conservative approach should be chosen in the early term phase, however, at the very latest since the

ARRIVE study, a larger scope of action considering the possibilities of induction of labor vs. conservative management is permissible during the full term phase. To better assess the perinatal risk of the aforementioned low-risk pregnancies and to avoid exceeding the due date on the basis of reliable, predictive markers for a PD-associated adverse perinatal outcome (APO), a “term screening” allowing the selection of cases with inapparent PD for induction of labor at full term (39 + 0 WG) would be optimal. In the following, the value and evidence supporting the use of fetomaternal Doppler ultrasound, fetal cardiac function indices and (anti-)angiogenic placental factors (sFlt-1, PlGF) as potential “screening tools” of the future shall be highlighted.

Fetomaternal Doppler Ultrasound

Investigations concerning the role of uterine Doppler ultrasound in the third trimester in the low-risk population (appropriate for gestational age – AGA: EFW \geq 10th percentile) demonstrate a clear association with uteroplacental dysfunction in the form of an increased uterine vascular resistance (mean uterine artery pulsatility index: mUtA-PI $>$ 95th percentile) and fetal cerebral blood flow redistribution, known as brain-sparing [26]. Furthermore, an increased mUtA-PI seems to be associated with a higher perinatal mortality regardless of the EFW, and therefore plays a relevant role in the context of prediction of perinatal mortality in addition to the EFW and the cerebroplacental ratio (CPR: PI of the middle cerebral artery [MCA]/PI of the umbilical artery [UA]) (► **Fig. 2**) [27].



Retro- as well as prospective studies on a large number of cases have described a correlation between a low CPR and an APO – independent of EFW [28–35]. Systematic meta-analyses confirmed the association between low CPR and APO in the low-risk population, although the predictive power of CPR was low with an overall low APO prediction rate [36,37]. Furthermore, the optimal CPR cut-off value in defining pathology is unclear (<5th percentile, <10th percentile, <20th percentile, multiple of the median [MoM], <1.1) and the results of previous studies are to be interpreted with regard to the time of CPR measurement and the study population [36,38]. In a recent study involving $n = 2052$ patients, Ortiz et al. was able to demonstrate that the risk for an emergency surgical delivery in the case of late-term delivery only significantly increased beyond $41 + 0$ WG with a CPR <10th percentile in the AGA population (39% vs. 20%; $p = 0.001$) [39]. The much-discussed use of the inverse CPR (umbilicocerebral ratio: UCR = UA-PI/MCA-PI) (► Fig. 2) instead of the CPR shall not be covered in detail at this point. The inversion of the CPR has a verifiably significant effect on the distribution and interpretation of the resulting UCR variables [40]. At first, the use of the UCR instead of the CPR seems problematic considering the extensively available literature concerning the CPR. Nonetheless, data from the TRUFFLE 2 feasibility study showed that in the late-onset FGR population, the UCR had a significant correlation with an APO and the usage of the UCR (instead of the CPR) is mathematically justified due to the fact that pathological UCR values reach into infinity while pathological CPR values move asymptotically towards 0 [41].

The idea of integrating the maternal side of the placenta into the Doppler-ultrasound-based APO risk assessment and the description of the fetal condition gave rise to the first studies that highlight the role of the cerebro-placental-uterine ratio (CPUR =

CPR/mUtA-PI) (► Fig. 2) in high- and low-risk populations [42–44]. In a population of $n = 347$ patients, Macdonald et al. was able to show for the first time that the CPUR had the strongest association with indicators for a late mild placental insufficiency and predicted more cases of FGR (BW <3rd percentile) compared to the CPR and/or mUtA-PI by itself [42]. A multicenter prospective study showed that in the low-risk population ($n = 804$) at term, too, there was a six-fold increase in the rate of emergency surgical delivery due to intrapartum fetal distress as well as a higher rate of APO in cases with a CPUR <10th percentile, even though the predictive power of the CPUR was moderate at best [43]. Morales-Rosello et al., however, could not determine an added predictive value of the CPUR with regard to APO when compared to the CPR in the low-risk population between $34 + 0$ – $41 + 0$ WG ($n = 891$) [44].

The currently available results concerning fetomaternal Doppler ultrasound in the low-risk population (AGA fetuses) and its association with an APO, in particular in late-term cases, raise the question of whether abnormal Doppler indices can or even should be cause for clinical consequences (even in the case of physiological amniotic fluid volume and CTG). Taking into account the current data around the added value of induction of labor in the low-risk population at term or late term [16–18], anomalies in the established fetomaternal Doppler indices should give rise to the consideration of whether the recommended offer of induction of labor at $41 + 0$ [20] in the S3 guideline should be a recommendation instead of an offer. At the very least, the authors believe that – if the fetomaternal Doppler ultrasound is properly used as part of the fetal monitoring in the low-risk population – an appropriate patient education and a participative form of decision-making should be employed when deciding on the timing of induction of labor during the late-term period.

Biomarkers – (Anti-)angiogenic Factors

Within the context of PE diagnostics, the sFlt-1/PlGF ratio has become a fixed component for diagnosis and an integral part of the national and international guidelines [45–48]. However, none of the randomized-controlled trials addressing the question of predicting (and improving) perinatal outcomes have to date evaluated the sFlt-1/PlGF ratio in pregnancies with PD (PE, FGR). The increasing tendency to use placental biomarkers to predict an APO in the PD population is reflected in recent work that observed an association between greatly elevated sFlt-1/PlGF levels (>655 in <34 + 0 WG, >201 in ≥34 + 0 WG) and an APO or a shortened time interval till delivery due to perinatal complications [49].

Preliminary work examining the value of (anti-)angiogenic factors in an unselected and low-risk near term population identified the potential of placental biomarkers to predict an APO. In a prospective (non-blinded) study (n = 795), Fiolna et al. analyzed the value of sFlt-1/PlGF determination (linked with the CPR and maternal risk factors) 24 h prior to induction of labor ≥37 + 0 WG. The authors did not find any added value using sFlt-1/PlGF with regard to the prediction of APO compared to only using maternal risk factors (+/- CPR). Nevertheless, a decreased PlGF serum level was significantly associated with an APO [50]. Another prospective blinded study (n = 207) of a low-risk population went through weekly PlGF and CPR measurements from 36 + 0 WG onwards. The aim of the study was to examine the predictive power of both PD markers relating to the indication for emergency surgical delivery due to intrapartum fetal distress. Bligh et al. were able to show that the combination of CPR and PlGF had a high predictive value in predicting emergency surgical delivery (sensitivity 100%, specificity 86%, false positive rate 14%). There was, however, no significant difference in the predictive power of CPR alone vs. the combination of CPR + PlGF [51]. Another prospective study of a late-term population (n = 426) determined that a PlGF < 5th percentile and sFlt-1/PlGF > 95th percentile was associated with a significantly shorter time interval until delivery (1.4 vs. 2.2 days) and used these results to generate reference values and sFlt-1 and PlGF percentile cut-offs for low-risk populations at >40 + 0 WG [52]. The same study group conducted a prospective blinded study to assess the incidence of a PD-associated APO depending on the level of sFlt-1/PlGF. The authors reported significantly lower PlGF serum levels in the APO group [53]. These results support the hypothesis that, even in the low-risk population, PlGF can be seen as a general marker for placental health, and its role in the prediction and reduction of PD-associated APO as a result of syncytiotrophoblastic stress should be evaluated further in randomized controlled trials [51, 53].

Fetal Cardiac Function

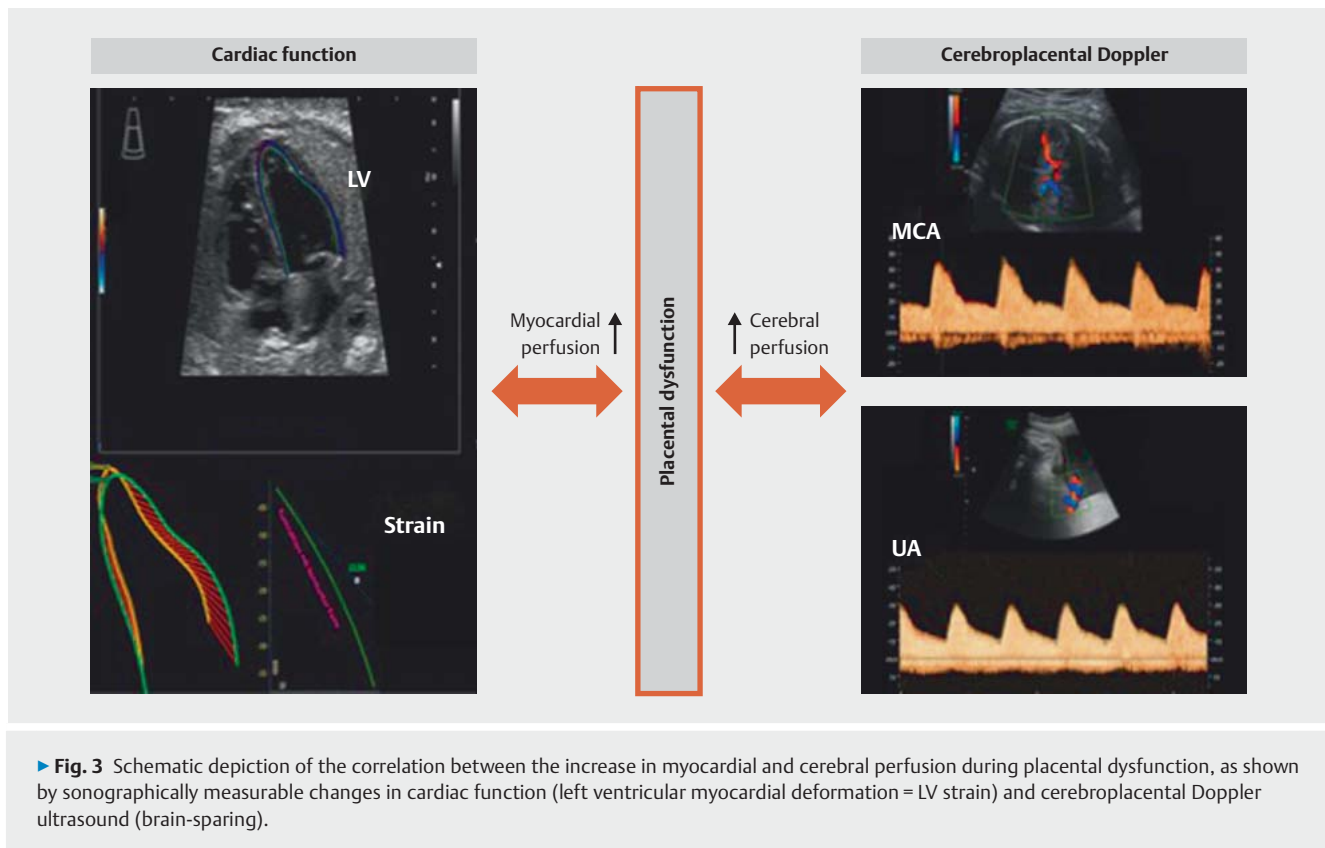
The fetal circulatory system is characterized by the adaptation of blood volume as needed in hypoxemic phases as a result of uteroplacental malperfusion. In these phases, there is a regulatory increase in blood flow to the adrenal glands, the brain and the myocardium [11]. This raises the question of the extent to which fetal cardiac function and cerebral perfusion are related in PD cases

(measured by sonography) (► Fig. 3). The redistribution of the cardiac output (CO), among other things (such as chemoreceptors), is responsible for the brain-sparing effect observed in times of fetal hypoxia [54, 55]. Echocardiographic examinations of hypoxic fetuses have shown that an increased cerebral perfusion is associated with a shift of the CO to favor the left ventricle (LV) [56, 57]. The cerebral blood flow redistribution and vasodilation leads to a decrease in the LV afterload, while the arterial vasoconstriction of the blood vessels of the lower body half increases the afterload of the right ventricle (RV) [58, 59]. With an increasing degree of intrauterine hypoxia, however, these cardiac compensatory mechanisms are exhausted, resulting in a decrease of the CO [60].

In a prospective observational study (n = 270) with patients at >36 + 0 WG, Alsolai et al. first examined the value of fetal cardiac function for predicting APO in a low-risk population. AGA fetuses that required an emergency surgical delivery due to intrapartum distress exhibited a lower LVCO, a higher RVCO and a lower CPR prenatally (measured within 2 weeks prior to delivery). Furthermore, the CPR and LVCO were significantly decreased in cases with an APO, and a positive correlation could be found between the LVCO and CPR [54].

In a follow-up study of the same study group, which examined further cardiac function indices and their association with APO or cerebroplacental Doppler indices, a correlation between the CPR or MCA-PI and the global left/right ventricular peak systolic strain (GLVPSS/GRVPSS), measured using the two-dimensional speckle tracking echocardiography (2D-STE), was shown [55]. 2D-STE is a technique for measuring fetal myocardial function independent of the angle of insonation. It is based on an image-to-image analysis that tracks the movement of so-called “speckles” within the myocardium and allows to assess systolic myocardial deformation (strain) during the cardiac cycle. The analysis is performed using a four-chamber view, usually offline in the form of a post-processing technique [61] (► Fig. 3). In the aforementioned study by Alsolai et al., the GLVPSS and GRVPSS values positively correlated with the CPR and MCA PI values. The strain measurement reflects the mechanics of myocardial movement, so that the correlation of cerebroplacental Doppler and the strain suggests a subtle fetal cardiac dysfunction at the time of cerebral blood flow distribution. However, this correlation, as associated with the need for emergency surgical delivery, could only be observed for GLVPSS and the CPR [55].

These results suggest that, in the context of a PD, the sonographically measurable cardiac function and the cerebral perfusion of the fetus are linked (► Fig. 3). In addition, there appears to be an association of subclinical fetal cardiac dysfunction with APO. This may potentially allow to stratify the low-risk population into pre- and intrapartum risk according to cardiac function measurements. The technical limitations of the cardiac function analysis due to factors such as fetal heart size, higher heart rates and motion artefacts, however, continue to present barriers to reproducibility. Therefore, the measured results and their clinical interpretation should be viewed critically [61]. Another limitation that must be considered at this point is the variability of strain anomalies: longitudinal strain values from SGA/FGR fetuses with a manifest PD have been measured as similar to, elevated and >95th percentile when compared to AGA fetuses [62, 63]. At this point in



time, the evidence required to confirm the added value of cardiac function analysis for predicting an APO, compared to the established fetal Doppler ultrasound, is lacking. Another question that has not yet been answered is whether the observed cardiac phenomena in PD cases are the result of adaptation and compensation or of impending decompensation of the fetus.

Ongoing Randomized Controlled Trials

One currently ongoing randomized controlled trial examining the role of (early term) PD screening in the low-risk population is the PROMISE trial. In the PROMISE trial (predicting intrapartum fetal compromise at term using the cerebroplacental ratio and placental growth factor levels), low-risk pregnant patients between 34 + 0 and 36 + 6 WG were randomized and assigned to two groups. Group 1 (the intervention group) was screened for PD (by CPR and PIGF) between 37 + 0–38 + 0 WG. Positive screen result patients (and thus high-risk patients: CPR < 20th percentile and PIGF < 33rd percentile) were then induced within 7 days. Negative screen result patients received standard care. Group 2 (control group) was not screened for PD but received standard care. The primary endpoint of the trial is to examine the effect of introducing an early term PD screening test (CPR + PIGF) to detect intrapartum fetal impairment for the purpose of reducing APO (emergency caesarean section, severe acidosis, 5-minute Apgar score ≤ 5 or perinatal death) [4]. The RATIO37 trial, performed by the Figueras study group, is also focusing on the area of early term PD screening. Among other things, its aim is to determine

whether induction of labor from 37 + 0 WG based on CPR as the sole indicator of a PD can improve the perinatal outcome in the low-risk population [62]. Before clinical decisions (especially those concerning the sensitive early term phase) are made on the basis of Doppler ultrasound and/or (anti-)angiogenic PD markers, the results of these above-named randomized controlled trials should be awaited and considered.

Summary

The remaining placental reserve capacity at term plays a decisive role in the perinatal morbidity of mother and child. Considering advances made in the field of fetal monitoring, the routine examination methods currently used at term or during the late-term period (CTG/amniotic fluid volume) may be insufficient to detect placental dysfunction (PD). Both established and new fetomaternal ultrasound parameters as well as (anti-)angiogenic factors may be helpful to detect subclinical PD (EFW > 10th percentile, normal CTG/amniotic fluid volume). To envisage "term screening" as a viable option, the general medical requirements for screening (prevalence, sensitivity/specificity, means of intervention) including the health policy and financial aspects (general availability, efficient cost-benefit analysis, low risk) need to be considered. For now, however, the value of these PD markers in the low-risk population in terms of the optimal delivery date needs to be examined in randomized controlled trials on a large number of cases.

Conflict of Interest

The authors declare that they have no conflict of interest.

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