Foetal Doppler Parameters as a Prognostic Marker Before Induction of Labour

Fetale Doppler-Parameter als prognostischer Marker vor Weheninduktion



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ABSTRACT

Introduction The value of foetal Doppler ultrasonography before induction of labour for prognostic assessment of the duration of labour and foetal outcome is presented.

Patients and Methods Doppler ultrasound of the foetal middle cerebral artery (MCA) and of the umbilical artery (UA) was performed in addition to evaluation of the Bishop score in 49 women around the expected date of confinement (38 + 0–42 + 0 weeks of gestation) prior to planned pharmacological induction of labour. These parameters were studied using

non-parametric statistical methods for associations with the duration of induction until delivery, the mode of delivery and foetal outcome.

Results The resistance index (RI) of the MCA (rs = 0.547, p < 0.001), but not the RI of the UA (rs = -0.055, p = 0.707) correlated positively with the duration of induction. Moreover, a negative correlation was found between the RI of the UA and the baby's arterial cord pH at birth (rs = -0.287, p = 0.046). No differences in the RI of MCA or UA were found between babies born vaginally and those delivered by secondary section.

Conclusion The present data show that Doppler measurement of the foetal MCA and UA before pharmacological induction of labour at term can be a further parameter for prognostic estimation of the duration and success of induction and of foetal outcome in addition to the established Bishop score.

ZUSAMMENFASSUNG

Einleitung Darstellung der Wertigkeit fetaler Doppler-Sonografie vor Weheninduktion zur prognostischen Einschätzung von Geburtsdauer und fetalem Outcome.

Patientinnen und Methoden Bei 49 Schwangeren um den errechneten Entbindungstermin (38 + 0–42 + 0 SSW) wurde vor geplanter medikamentöser Weheninduktion neben der Evaluation des Bishop-Scores eine Doppler-Sonografie der fetalen A. cerebri media (ACM) sowie der A. umbilicalis (AU) durchgeführt. Diese Parameter wurden mittels nicht parametrischer statistischer Methoden auf Assoziationen mit der Einleitungsdauer bis zur Geburt, dem Geburtsmodus und dem kindlichen Outcome untersucht.

Ergebnisse Der Resistenz-Index (RI) der ACM (rs = 0,547, p < 0,001), nicht aber der RI der AU (rs = -0,055, p = 0,707) korrelierte positiv mit der Einleitungsdauer. Zudem zeigte sich eine negative Korrelation zwischen dem RI der AU und dem kindlichen arteriellen Nabelschnur-pH bei Geburt (rs = -0,287, p = 0,046). Zwischen Kindern, die vaginal geboren wurden, und denen, die per sekundärer Sectio entbunden wurden, fanden sich keine Unterschiede im RI von ACM oder AU.

Schlussfolgerung Die vorliegenden Daten zeigen, dass neben dem bereits etablierten Bishop-Score die Doppler-Messung der fetalen ACM sowie der AU vor medikamentöser Weheninduktion am Termin ein weiterer Parameter zur prognostischen Abschätzung von Einleitungsdauer und -erfolg sowie dem kindlichen Outcome sein kann.

Introduction

In Germany, roughly 20–25% of all births are induced pharmacologically, and up to 35% in the Anglo-American countries [1,2]. The indications include post-term pregnancy, underlying maternal disease such as pre-eclampsia or diabetes mellitus, maternal exhaustion, suspected foetal macrosomia, subjectively sluggish foetal movements or a suspect CTG. Pharmacological induction of labour, unlike spontaneous delivery, harbours a roughly 2.2 times increased risk of secondary caesarean section [2], and the duration of induction is often difficult to predict.

The cervical Bishop score is generally used to assess the success of induction [3]. However, this has only limited predictive value as regards the potential need for secondary caesarean section: with a Bishop score of 4, 5, 6 and 9, the sensitivity and specificity are 47%/75%, 61%/53%, 78%/44% and 95%/30% respectively [4].

While the resistance index (RI) of the foetal aorta remains relatively constant over the course of pregnancy, the resistance of the umbilical artery (UA) and middle cerebral artery (MCA) diminishes. Severi et al. showed in 2008 that both low pulsatility indices (PI) and low resistance in the foetal MCA are indicators that the onset of labour is approaching [5].

The aim of this study was to find additional predictive parameters for prognostic assessment of the success of pharmacological induction. Prior to pharmacological induction of labour at term, Doppler measurement of the foetal UA and MCA was performed in addition to evaluation of the Bishop score. The results were correlated with the duration of induction until delivery, the mode of delivery and the foetal outcome. Additional subgroup analyses were performed according to parity (primi- vs. multiparity) and weeks of gestation at the start of induction ($\leq 41 + 0$ vs. > 41 + 0), since both factors may have an influence on the duration of induction and the association between induction duration and Doppler results.

Patients and Method

Patient recruitment

49 patients over 18 years with an uncomplicated singleton pregnancy, who presented in our perinatal centre between October 2012 and April 2013 for induction of labour at the estimated date of confinement (38 + 0 - 42 + 0 weeks), were included in the study. Patients with

- 1. Maternal diseases such as diabetes mellitus or pre-eclampsia,
- 2. Ultrasonographic morphological or genetic foetal anomalies,
- 3. Foetal growth restriction or suspected macrosomia and

4. Pathological foetal Doppler and/or pathological CTG

were excluded from the study. The established estimated due date was checked using the crown-rump length (CRL) in the first-

trimester ultrasound scan and corrected according to the CRL if there was a discrepancy of more than 7 days [6].

Since the German guideline on "Management of overdue and post-term pregnancy" (DGGG 2010) and the National Institute of Clinical Excellence (NICE) in its clinical guideline on induction of labour (2008) recommend induction after 41 + 0 weeks regardless of other maternal and/or foetal factors, we also analysed the subgroup of patients over 41 + 0 weeks.

Data collection

Immediately before planned induction of labour, the cervical dilation in cm and the Bishop score were determined [3]. This was followed by Doppler ultrasound scan of the foetal UA and MCA using the high-resolution ultrasound Voluson Expert 730 System, GE Voluson e[®] or GE Voluson Expert 8[®], General Electrics, GE Medical Systems, Solingen, Germany. The ultrasound scans were evaluated by 2 trained ultrasound experts (at least DEGUM I level); for both the resistance index (RI) of the foetal UA and the RI of the MCA, the mean of 3 consecutive single measurements was recorded through our internal hospital Viewpoint System (version 5). Since the blood flow patterns of the foetal vessels and thus the measured resistance in the vessels in pregnancy depend on the week of gestation [7], the RI of the arteries was divided by the mean corresponding to the gestational age to allow better comparability and shown as MoM (multiple of the median) [8]. The duration of induction was measured from the first dose of the medication given to induce labour until the delivery of the baby. The mode of delivery and arterial cord pH as a measure of foetal outcome were documented immediately after delivery. The data were analysed retrospectively from the files in 23 cases and prospectively in 26 cases in the context of the induction.

Statistical analysis

IBM SPSS Statistics for Windows, Version 22 (IBM Corporation, New York, USA) was used for statistical analysis. Since the data for the variables analysed in this study (age and BMI of the mother, cervical dilation, duration of induction, RI values) were not normally distributed, non-parametric statistical methods exclusively were used for the analysis. Group comparisons were made by means of the Mann-Whitney U test (for two groups) and the Kruskal Wallis H test in the case of more than two groups. Correlation analyses were performed using the Spearman rank correlation coefficient. A general linear model was used for multivariate analysis of the influence of cervical dilation and Bishop score and of the UA and MCA resistance indices on the duration of induction. In the first step, a model with cervical dilation or Bishop score and the additional maternal parameters age (years), body mass index (BMI, kg/m²) and parity (primipara, multipara) was analysed. The next step was to examine whether addition of the RIs of the UA or MCA significantly improves the model (significance of the change of the F statistics), that is, whether addition of the RI enables significantly better prediction of the duration of induction. The accuracy of the statistical models was evaluated using the adjusted determination coefficient R². The R² value states which proportion of the observed variance in duration of induction can be explained by the model; the adjusted R² value takes the complexity of the underlying statistical model into account [9, 10]. All stated p values are two-sided, and the significance level was set at α = 0.05. The study meets the standards of the Declaration of Helsinki, and approval to conduct the study was obtained from the ethics committee of Ulm University (no. 325/13).

Results

Patient characteristics, indication and induction procedure

In this study, 21 primiparas and 28 multiparas were induced. The average BMI of the study patients was 25.6 kg/m² (range 18.4-39.7 kg/m²) and the average maternal age was 30.2 years (range 20-41 years). The most frequent indications for induction were post-term pregnancy (n = 31), subjectively sluggish foetal movements (n = 7) or a suspect CTG (n = 7) when the ultrasound was otherwise normal, the patient's wish to end the pregnancy because of maternal exhaustion in 2 cases, and ultrasound suspicion of a relative disparity if the pregnancy was continued. Pharmacological induction was with misoprostol in 29 cases (dosage: initial dose of 50 µg orally, followed by 75 µg every 4 hours), with Minprostin gel in 15 women who had had a previous section (dosage: initial dose of 1 mg, repeated every 6 hours, total 3 times/day), and with a combination of the two drugs in 3 cases. Misoprostol (see above) was given first, and if there had been no essential progress in labour after up to 10 doses, further priming was continued with Minprostin gel. Two multiparas with an advanced Bishop score of \geq 5 received an oxytocin infusion (dosage: 3 IU oxytocin in 250 NaCl at an initial dosage of 10 ml/hour, increased individually). 40 women (81.6%) had vaginal delivery (33 spontaneous, 7 assisted) and 9 women (18.4%) were delivered by secondary caesarean section. The median Bishop score obtained immediately before induction of labour was 4 (range 1–9). The median cervical dilation was 1 cm (range 0-5 cm); cervical dilation of more than 2 cm was found in 2 cases (4.1%). The mean duration of induction was 25.2 h (median 19 h, range 4.5-57.3 h). The maternal parameters at the time of inclusion in this study, the RI data from the Doppler measurements and the induction and delivery data are summarised in > Table 1.

Associations with duration of induction

The duration of induction did not differ significantly between primiparas and multiparas (multiparas: median 27.5 h, range 4.5– 57.3 h; multiparas: median 16.3 h, range 8.5–49.0 h; p = 0.203) and between vaginal delivery and secondary section (vaginal deliveries: median 17.4 h, range 8.0–54.0 h; deliveries by secondary section: median 30.5 h, range 4.5–57.3 h; p = 0.214). There were also no significant differences in the duration of induction between the four different induction methods (p = 0.132) or between inductions started before or after weeks 41 + 0 (p = 0.204). Neither maternal age (r_s = -0.125, p = 0.391) nor **Table 1** Patient parameters, induction data and Doppler ultrasound data at the start of induction (n = 49).

Age (years)	Mean ± SD	30.2 ± 5.8
	Median	31
	Range	20-41
Body mass index (kg/m²)	Mean ± SD	25.6 ± 4.9
	Median	24.8
	Range	18.4–39.7
Parity	Primipara	28 (57.1%)
	Multipara	21 (42.9%)
Indication for induction	Post-term pregnancy	31 (63.3%)
	Sluggish foetal movements	7 (14.3%)
	Suspect CTG	7 (14.3%)
	Other	4 (8.2%)
Weeks of gestation at the start of induction	≤41+0	38 (77.6%)
	>41+0	11 (22.4%)
Induction method	Tablets	29 (59.2%)
	Gel	15 (30.6%)
	Tablets plus gel	3 (6.1%)
	Oxytocin	2 (4.1%)
Cervical dilation at the start of induction (cm)	0	17 (34.7%)
	1	21 (42.9%)
	2	9 (18.4%)
	3	1 (2.0%)
	5	1 (2.0%)
Bishop score at the start of induction	1	5 (10.2%)
	2	4 (8.2%)
	3	10 (20.4%)
	4	8 (16.3%)
	5	8 (16.3%)
	6	7 (14.3%)
	7	1 (2.0%)
	8	4 (8.2%)
	9	1 (2.0%)
	Missing	1 (2.0%)
Resistance index of the umbilical artery (MoM)	Mean ± SD	0.99 ± 0.13
	Median	0.96
	Range	0.76-1.45
Resistance index of the middle cerebral artery (MoM)	Mean ± SD	0.95 ± 0.09
	Median	0.95
	Range	0.76-1.14
Induction duration (h)	Mean ± SD	25.2 ± 15.8
	Median	19.0
	Range	4.5-57.3
Mode of delivery	Spontaneous	33 (67.3%)
	Vacuum extraction	7 (14.3%)
	Secondary section	9 (18.4%)



Fig. 1 Correlation between induction duration in hours and a Bishop score at induction of labour ($r_s = -0.395$, p = 0.005); b cervical dilation (cm) at induction of labour ($r_s = -0.398$, p = 0.005).

BMI ($r_s = 0.135$, p = 0.366) correlated significantly with the duration of induction. In all pregnant women, there was a negative correlation between the duration of induction and the Bishop score obtained immediately before induction of labour ($r_s = -0.395$, p = 0.005; \blacktriangleright **Fig. 1 a**). The initial cervical dilation, which is a single parameter in the Bishop score that is easy to measure, likewise showed a significant negative correlation with the duration of induction ($r_s = -0.398$, p = 0.005) (\triangleright **Fig. 1 b**).

The higher the resistance (RI) of the MCA before the start of induction, the longer the time from the start of induction until delivery of the baby ($r_s = 0.547$, p < 0.001). This was the case for both primiparas ($r_s = 0.606$, p = 0.004) and multiparas ($r_s = 0.505$, p = 0.006; Fig. 2a). A subgroup analysis according to gestation week at the start of induction showed a significant positive association between the RI of the MCA before the start of induction and the duration of induction for inductions started \leq week 41 + 0 (r_s = 0.593, p < 0.001), but not for inductions started >week 41 + 0 (r_s = 0.274, p = 0.415; **Fig. 2b**). Unlike MCA resistance, there was no significant correlation between the resistance of the UA measured before induction of labour and the duration of induction ($r_s = -0.055$, p = 0.707). The RI of the UA and MCA measured at the start of induction did not differ significantly between inductions where delivery was vaginal and those in which secondary section was performed (both p > 0.3).

A multivariable model with induction duration as dependent variable and Bishop score together with the maternal parameters age, BMI and parity as independent factors showed that the Bishop score had a significant effect on the duration of induction (p = 0.022). A similar result was apparent when the model included cervical dilation instead of the Bishop score (p = 0.018). Addition of the RI of the UA did not result in a significant improvement either for the model with the Bishop score or for the model with cervical dilation (both p > 0.05). By contrast, a statistical improvement resulted for both the model with the Bishop score and for the model with cervical dilation when the RI of the MCA was

added (both p = 0.002). The model with Bishop score, RI of the MCA and the maternal parameters age, BMI and parity together explains 27.9% of the observed variance of the induction duration (adjusted R² = 0.279; adjusted R² without RI of the MCA = 0.105), while the model with cervical dilation, RI of the MCA and the maternal parameters age, BMI and parity explains 28.3% of the observed variance of the induction duration (adjusted R² = 0.279; adjusted R² without RI of the MCA = 0.114). The maternal parameters parity, age and BMI, on the other hand, were not associated significantly with the duration of induction in any of the models (all p > 0.05).

When the multivariable model is calculated with induction duration as dependent variable and Bishop score or cervical dilation together with the maternal parameters age, BMI and parity as independent factors excluding patients with start of induction in weeks > 41 + 0, some markedly higher determination coefficients are obtained despite the associated reduction in the sample size from 49 to 38 patients. The model with Bishop score, RI of the MCA and the maternal parameters age, BMI and parity together explains 47.7% of the observed variance of the induction duration (adjusted R² = 0.477; adjusted R² without RI of the MCA = 0.242), while the model with cervical dilation, RI of the MCA and the maternal parameters age, BMI and parity explains 45.2% of the observed variance of the induction duration (adjusted R² = 0.452; adjusted R² without RI of the MCA = 0.255).

Foetal outcome

There was no significant association between the duration of induction and the foetal outcome measured by the postnatal arterial cord pH ($r_s = -0.131$, p = 0.371). While no association between the resistance index of the MCA and the foetal outcome was found ($r_s = 0.010$, p = 0.945), there was a significant negative correlation between UA resistance and foetal outcome ($r_s = -0.287$, p = 0.046). The higher the RI of the UA antenatally at the start of induction, the lower the arterial cord pH post partum (**> Fig. 3**).



Fig. 2 Correlation between induction duration in hours and resistance index of the middle cerebral artery (MoM) at induction of labour depending on a parity (primiparas: $r_s = 0.606$, p = 0.004; multiparas: $r_s = 0.505$, p = 0.006); b weeks of gestation at the start of induction (\leq 41 + 0: $r_s = 0.593$, p < 0.001; >41 + 0: $r_s = 0.274$, p = 0.415).

When patients with the start of induction in weeks > 41 + 0 were excluded, there was still no significant association between the resistance index of the MCA and foetal outcome measured by the postpartum arterial cord pH ($r_s = -0.026$, p = 0.876), while the correlation coefficient for the association between the resistance index of the UA and the foetal outcome was increased despite the reduced number of patients ($r_s = -0.393$, p = 0.015).

Discussion

The duration of pregnancy, calculated from the first day of the last menstrual period, is approximately 40 weeks. Prolongation of pregnancy beyond the estimated date of delivery (EDD) harbours the risk of placental insufficiency with the consequent risk of intrauterine foetal death [11, 12].

In 2013, Stuck et al. conducted a survey of 54 perinatal centres in Germany. This showed that misoprostol is the agent of first choice for induction of labour in 37 (68.5%) clinics provided surgery on the uterus had not been performed previously [13]. There was remarkable heterogeneity with regard to administration route, dosage, total daily dosage and interval between individual doses and in the overall duration of use [13]. Like most centres, we mainly used misoprostol in our study, and used Minprostin gel if induction was unsuccessful or the patient had previously had a section. Two patients with a Bishop score \geq 5 before the start of induction were given an oxytocin infusion from the outset.

Many different factors influence the success of pharmacological induction of labour at term. Our cohort demonstrated a significant positive correlation with the duration of induction for both the Bishop score measured prior to induction and for the individual parameter "cervical dilation" contained in the Bishop score. This result correlates with the available literature [14–16].

Gonen et al. showed in 1998 that parity can serve as a predictive factor for the duration from the start of induction until deliv-



▶ Fig. 3 Correlation between the resistance index of the umbilical artery (MoM) at induction of labour and the postpartum arterial cord pH (r_s = -0.287, p = 0.046).

ery, in addition to the Bishop score [17]. We found a nominally shorter induction duration for multiparas compared with primiparas in our group of patients (median 16.3 vs. 27.5 h), but the difference did not reach significance, due to the relatively small number of patients.

Since there is often great uncertainty with regard to the success of induction of pregnant women, especially when the cervix is still unripe, additional predictive parameters for better assessment of success are required, especially when weighing induction against primary caesarean section as alternative modes of delivery.

The hypothesis underlying this study was the assumption that measurement of foetal Doppler parameters might possibly provide an addition criterion for assessing the duration and success of induction. However, changes in resistance in the middle cerebral artery at an early gestational age must be distinguished from those at term. The changes in Doppler parameters known to occur with intrauterine growth retardation ("brain sparing"; defined as RI in the umbilical artery >90 percentile and RI in the middle cerebral artery < 10%) are pathological and a reaction of the foetal circulation to impending foetal hypoxia. This contrasts with the so-called "term effect" of a fall in the RI and PI of the MCA, which is a physiological process [5]. As the foetal head descends into the mother's pelvis before the expected date of delivery, there is a physiological fall in the resistance in the middle cerebral artery, to allow increasing oxygenation of brain structures [18]. Another assumption is that this also triggers oxytocin secretion from the foetal pituitary, which stimulates labour. This might also explain the phenomenon of premature labour in the case of foetuses with intrauterine growth retardation, in the sense of an autoregulation mechanism, so as to avoid intrauterine death in these pregnancies. It would be interesting to compare the prepartum resistance of the MCA between babies with breech presentation and babies with cephalic presentation [19].

Assessment of resistance in the umbilical artery, the estimated foetal weight, amniotic fluid volume and biophysical profile help to distinguish the "term effect" from pathological centralisation of the foetal circulation in the form of "brain sparing". For foetuses with very low resistance in the MCA and/or other abnormalities, e.g., on cardiotocography, pharmacological induction should be regarded critically and primary caesarean section should possibly be considered instead.

Doppler ultrasound assessment of the foetal MCA is a test that can usually be performed readily as part of the biometric measurements of a baby prior to planned induction of labour. In our patients, a significant positive correlation was apparent between the RI (MoM) of the foetal MCA measured before induction and the duration of induction; the higher the prepartum RI of the MCA, the longer the duration of induction. The multivariable analysis adjusted for the maternal parameters age, BMI and parity showed that cervical dilation and resistance in the MCA exert an influence on the duration of induction independent of one another. The two variables together explain approximately 30% of the observed variance of induction duration. A similar result is apparent when the Bishop score is used instead of cervical dilation in the multivariable analysis.

Since the German guideline on "Management of overdue and post-term pregnancy" (DGGG 2010) and the National Institute of Clinical Excellence (NICE) in its clinical guideline on induction of labour (2008) recommend induction after 41 + 0 weeks regardless of other maternal and/or foetal factors, we also analysed the subgroup of patients over 41 + 0 weeks. This showed a significant positive association between the RI of the MCA before the start of induction and induction duration for inductions started \leq 41 + 0 weeks but not for inductions started > 41 + 0 weeks. When the multivariable model is calculated with induction duration as dependent variable and Bishop score or cervical dilation together with the maternal parameters age, BMI and parity as independent factors excluding patients with start of induction in weeks > 41 + 0, markedly higher determination coefficients are obtained despite the associated reduction in the sample size from 49 to 38 patients. The model with Bishop score, RI of the MCA and the maternal parameters age, BMI and parity together then explains 47.7% of the observed variance of the induction duration, while the model with cervical dilation, RI of the MCA and the maternal parameters age, BMI and parity explains 45.2% of the observed variance of the induction duration.

In our study, no correlation was shown between the RI of the UA and the time from the start of induction of labour until delivery, and there were no significant differences in the RI of the UA measured at the start of induction between inductions where delivery was vaginal and inductions in which delivery was by secondary section. However, there was a significant association between the RI of the UA and the arterial cord pH of the neonate. Babies with a prepartum umbilical RI in the upper normal range showed significantly worse arterial cord pH post partum. Since the resistance of the UA provides information about placental function and thus about the intrauterine supply of the foetus, increased resistance in the UA explains a relative impairment of placental function and therefore supply to the foetus [20, 21]. Unlike the UA, this study did not find any association between the RI of the MCA measured at the start of induction and the baby's postpartum arterial cord pH. This result is consistent with studies in which an association between RI in the MCA and the foetal outcome was found only in risk populations [22, 23].

In summary, this study shows that Doppler examination of the MCA at the start of induction can provide additional information about the probable duration of induction in addition to the parameters used clinically to date such as Bishop score or cervical dilation and parity to estimate the duration and success of induction of labour at term. Doppler measurement of the UA at the start of induction allows prognostic assessment of the postnatal foetal outcome. The MCA and Bishop score have an independent influence on the duration of induction, but in our study they can explain about 30% of the variation in induction duration, but about 45% when patients whose induction is started in weeks > 41 + 0 are excluded. However, our study is based on a small number of patients and therefore has low statistical power.

Other limitations of the study consist of the heterogeneity of the patients with regard to parity, indication for induction, drug employed and the fact that some of the data were obtained retrospectively and some prospectively. However, this better reflects the real situation in routine clinical practice than would be the case in a prospective study with uniform induction indications and methods. Further and larger studies are necessary, however, to further optimise the prognostic conclusion regarding induction duration and success at term and develop an algorithm consisting of

- 1. Parity
- 2. Bishop score or cervical dilation and
- 3. MCA results.

Another possible study would be to compare the prepartum RI of the MCA between babies with breech presentation and those with cephalic presentation to investigate the underlying regulatory mechanisms. Ideally, this would deliver evidence about the course and success of induction in pregnant women at term, which might enable the mode of delivery likely to be successful to be planned prospectively.

Conclusion for Practice

When estimating the duration of induction at term, Doppler measurement of the middle cerebral artery appears to be an additional prognostic factor in addition to the established Bishop score. The resistance in the umbilical artery correlated with the foetal arterial cord pH.

Conflict of Interest

The authors declare that they have no conflict of interest.

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