Kardiovaskuläre hämodynamische Veränderungen nach antenatalenKortikosteroiden bei Feten mit intrauteriner Wachstumsretar-dierung und bei zeitgerecht entwickelten Feten

Marchi, Laura; Pasquini, Lucia; Elvan, Ayten; Bilardo, Caterina Maddalena

Published in:
Ultraschall in der Medizin

DOI:
10.1055/a-0654-4824

Publication date:
2020

Thieme

Cardiovascular Hemodynamic Changes After Antenatal Corticosteroids in Growth Restricted and Appropriate for Gestational Age Fetuses

Kardiovaskuläre hämodynamische Veränderungen nach antenatalen Kortikosteroiden bei Feten mit intrauteriner Wachstumsretardierung und bei zeitgerecht entwickelten Feten

Authors
Laura Marchi[1], Lucia Pasquini[1], Ayten Elvan-Taspinar[2], Caterina Maddalena Bilardo[3]

Affiliations
1 Department for Women and Child Health, Azienda Ospedaliera Universitaria Careggi, Firenze, Italy
2 Department of Obstetrics, University Medical Center Groningen, University of Groningen, Netherlands
3 Department of Obstetrics, Vrije Universiteit Amsterdam, Netherlands

Key words
obstetrics, doppler, antenatal corticosteroids, fetal growth restriction

received 08.01.2018
accepted 26.06.2018

Bibliography
DOI https://doi.org/10.1055/a-0654-4824
Published online: 2018
Ultraschall in Med

ISSN 0172-4614

Correspondence
Dr. Laura Marchi
Department for Women and Child Health, Azienda Ospedaliera Universitaria Careggi, Largo Brambilla, 3, 50141 Firenze, Italy
Tel.: ++ 39/55/7 94 93 68
laura.marchi84@gmail.com

ABSTRACT

Purpose To investigate hemodynamic effects after antenatal corticosteroids (ACS) administration in appropriate for gestational age (AGA) and early growth restricted (GR) fetuses by measurement of Doppler cardiovascular function parameters.
Materials and Methods Prospective cohort study. AGA and GR singleton pregnancies receiving ACS for fetal lung maturation between 24 + 0 – 33 + 6 weeks were enrolled. Feto-placental vascular hemodynamics were studied by: umbilical artery (UA) pulsatility index (PI), middle cerebral artery (MCA) PI, renal artery (RenA) PI. Cardiac function was evaluated by ductus venosus (DV) PI and by echocardiographic parameters: E to A wave ratios (E/A) and mitral and tricuspid annular plane systolic excursion (MAPSE and TAPSE) for diastolic function, left and right myocardial performance index (MPI) for overall (diastolic and systolic) function. A single operator performed all the measurements at 3 different time points (E): E0 before or within 4 hours of ACS administration (baseline examination), E1 24 – 48 hours after the first dose and E2 7 days after the second dose of ACS. The values were expressed as z-scores. Pairwise comparisons with paired t-test were performed to compare measurements before and after exposure to ACS.
Results 25 AGA and 20 GR fetuses (mean gestational age: 31 + 1 and 30 + 6, respectively) were included in the analysis. In the AGA group ACS administration was associated with a significant reduction in UA PI. In the GR fetuses ACS temporarily (E0-E1) restored UA-end diastolic flow (EDF) in 6 of 9 fetuses with A/R-EDF ("Return of EDF phenomenon") and produced a significant increase (worsening) in right MPI (both in E1-E2 and in E0-E2).
Conclusion ACS administration is associated with UA vasodilation in both AGA and GR fetuses and with an increase in right MPI in the latter group. This suggests a worsening in cardiac function in GR fetuses.

ZUSAMMENFASSUNG

Ziel Untersuchung der hämodynamischen Effekte nach Verabreichung von antenatalen Kortikosteroiden (ACS) in bei zeitgerecht entwickelten AGA-Feten („appropriate for gestational age") und bei Feten mit früher intrauteriner Wachstumsretardierung (GR) durch Messung von kardiovaskulären Funktionsparametern in der Dopplersonografie.
Material und Methoden In die prospektive Kohortenstudie wurden AGA- und GR-Einlings-Schwangerschaften von SSW 24 + 0 bis 33 + 6 eingeschlossen, die ACS für die fetale Lungenreifung erhielten. Die Untersuchung der fetoplazentaren vaskulären Hämodynamik erfolgte durch: Pulsatilitätsindindizes (PI) der A. umbilicalis (UA), der A. cerebri media (MCA) und der Nierenarterie (RenA). Die Herzfunktion wurde durch den PI des Ductus venosus (DV) und durch echokardiografische

Parameter ausgewertet: Ratio von E- zu A-Welle (E/A) und die „Mitral and Tricuspid Annular Plane Systolic Excursion“ (MAPSE und TAPSE) für die diastolische Funktion, linker und rechter „Myocard Performance Index“ (MPI) für die Gesamtfunktion (diastolisch und systolisch). Ein einzelner Untersucher führte alle Messungen zu drei verschiedenen Zeitpunkten (E) durch: E0 vor oder innerhalb von 4 Stunden nach ACS-Gabe (Basisuntersuchung), E1 24 – 48 Stunden nach der ersten Dosis und E2 sieben Tage nach der zweiten ACS-Dosis. Die Werte wurden als Z-Scores angegeben. Paarweise Vergleiche erfolgten mittels gepaarten t-Test, um Messungen vor und nach ACS-Exposition zu vergleichen.

Ergebnisse 25 AGA- und 20 GR-Feten (mittlere SSW 31 + 1 bzw. 30 + 6) wurden in die Analyse einbezogen. In der AGA-Gruppe war die ACS-Gabe mit einer signifikanten Reduktion des UA PI assoziiert. Bei GR-Feten stellte ACS bei 6 von 9 Feten mit A/R-EDF („Return of EDF-Phänomen“) den UA-end diastolischen Fluss vorübergehend (E0-E1) wieder her (EDF) und führte zu einer signifikanten Erhöhung (Verschlechterung) des rechten MPI (sowohl bei E1-E2 als auch bei E0-E2).

Schlussfolgerung Eine ACS-Gabe ist sowohl bei AGA- als auch bei GR-Feten mit einer UA-Vasodilatation assoziiert, und bei Letzteren auch mit einem Anstieg des rechten MPI. Dies deutet auf eine Verschlechterung der Herzfunktion bei GR-Feten hin.

Introduction

Antenatal corticosteroids (ACS) administration for accelerating fetal lung maturation is the standard of care in all women at risk for preterm delivery [1]. This treatment is suggested to evoke hemodynamic changes in the feto-placental circulation that differ in appropriate for gestational age (AGA) fetuses and in growth restricted (GR) ones, a subgroup accounting for 2 – 4 % of preterm births. Authors are concordant in showing a vasodilatory effect of ACS in GR fetuses, not documented in the AGA group [2]. The mechanisms underlying these different responses are still to be determined [3].

The clinical significance of these modifications has to be ascertained too, especially in the GR group. It is well known that the GR fetus undergoes cardiovascular modifications, such as arterial blood flow redistribution and hypertensive response to increase in after-load, to cope with hypoxia and increased placental resistance [4]. There is growing concern about the possible interference of ACS in this circulatory adaptation [5]. It also unclear whether the beneficial effects of exogenous ACS administration in AGA fetuses also apply to GR fetuses, in which endogenous corticosteroids release may promote lung maturation. This issue has not yet been specifically investigated [6].

Hemodynamic changes produced by ACS have been studied in the human fetus mainly by Doppler waveform indices of downstream resistance to flow, focusing especially on umbilical and middle cerebral artery pulsatility indexes [2] and rarely examining other vascular districts, although color flow mapping has eased the investigation of the whole fetal vascular system. In addition, even though functional echocardiography has made it possible to examine fetal cardiac hemodynamics in several conditions [7], only two studies have thus far evaluated cardiac functional parameters after ACS. The first one, performed in AGA fetuses, showed no modification of the E wave/A wave ratios [8] within 72 hours after ACS, whereas the second demonstrated an improvement in the right myocardial performance index (MPI) in late GR fetuses 24 hours after ACS administration [9]. No study is currently available on the long-term effects of ACS on these indexes in both populations.

The aim of this study was to analyze the hemodynamic modifications after ACS in both AGA and early GR fetuses by investigating both vascular parameters and cardiac function. We postulate that the changes produced by ACS may be transient, appearing soon after administration, and that they may be different in the two subgroups.

Methods

This prospective cohort study was conducted at a tertiary referral hospital (Azienda Ospedaliero-Universitaria Careggi -AOUC- Florence, Italy). The study was approved by the local hospital ethics committee (CEAVC protocol number 16.275)

Women with singleton pregnancies between 24^{+0} and 33^{+6} weeks receiving ACS (Betamethasone 12 mg i. m. 2 doses 24 hours apart) for fetal lung maturation according to the hospital protocol were enrolled in the study. Gestational age was determined by first-trimester ultrasound scan. GR fetuses were defined by an abdominal circumference (AC) or an estimated fetal weight (EFW) below the 10^{th} percentile for gestational age according to local reference or a significant deflection in their growth curve – > 2 quartiles [10]. The AGA group comprised fetuses with an EFW ≥ 10^{th} percentile and an AC ≥ 10^{th} percentile and a normal growth pattern. Fetuses with major structural defects or abnormal karyotype were excluded.

Placental vascular hemodynamics were studied by umbilical artery (UA) pulsatility index (PI).

Fetal vascular hemodynamics were investigated by middle cerebral artery (MCA) PI, indicative of brain sparing, and renal artery (RenA) PI, representing the non-spared circulation. The cerebro-placental ratio (CPR) was also calculated.

Cardiac function was evaluated by ductus venosus (DV) PI and by echocardiographic functional parameters: E to A wave ratios (E/A), mitral and tricuspid annular plane systolic excursion (MAPSE and TAPSE) for the diastolic function and left and right myocardial performance index (MPI), for the overall (diastolic and systolic) cardiac function.

The PIs of UA, MCA and DV were measured as described in the literature [11, 12]. The presence, absence (A) or reversal (R) of the

end-diastolic flow (EDF) in the UA and of the a-wave in the DV were also recorded. The CPR was calculated as previously reported [11].

Renal arteries were identified with power Doppler in a coronal plane through the fetal trunk showing both kidneys. Pulsed Doppler evaluation was performed with a sample volume of 2 mm and an angle of incidence between 0°-30°. The PI values were calculated by the built-in computer software of the ultrasound equipment after manual tracing of the outer envelope of at least 3 waveforms over the entire cardiac cycle [13].

Cardiac parameters were obtained by conventional pulsed Doppler or by M-mode, keeping an insonation angle of the ultrasound beam as close to 0° as possible with respect to the direction of blood flow.

Mitral and tricuspid E/A ratios were obtained measuring the peak early (E) and late (A) trans-valvular filling velocities obtained from a basal or apical four-chamber view, placing the sample volume just below the valve leaflets [14].

MAPSE and TAPSE were measured in real time in an apical or basal four-chamber view, with the cardiac apex at 12 or 6 o'clock. The M-mode beam was aligned through the lateral side of the valve annulus, parallel to the interventricular septum. The maximum amplitude of motion was taken as the extent of displacement between end-systole and end-diastole, measured in millimeters. Measurements were performed 'up-up' on the M-mode trace [15].

The left MPI was measured at the level of the left ventricular outflow tract view, illustrating the four chambers of the heart and the aorta arising from the left ventricle. The sample volume was placed to include both the ascending aorta and the mitral valve where the clicks corresponding to the opening and closing of the two valves could be clearly visualized. The isovolumetric contraction time (ICT), isovolumetric relaxation time (IRT) and ejection time (ET) were calculated using the beginning of the mitral and aortic valve clicks as landmarks and the MPI was calculated as (ICT+IRT)/ET [16]. The right MPI was calculated as follows: ejection time of the right ventricle was obtained by placing the Doppler sample volume within the pulmonary artery, distal to the pulmonary valve, in a transverse view of the heart including the artery arising from the right ventricle. The total right systolic time was measured obtaining the flow through the tricuspid valve from the end of an E/A waveform to the beginning of the next E/A waveform. The MPI was calculated by dividing the isovolumetric time (IVT), which is the whole systolic time minus the ET, by the ET. To be sure that different heart rates would not affect the final MPI calculation, the systolic time and the ET were calculated in heart cycles with a similar heart rate [17]. The settings used to assess the MPIs were sweep speed 5, gain -10 dB and WMF 210 Hz, as suggested by Lobmaier et al. as the best to increase reproducibility [18].

Ultrasound examinations were performed using a GE Voluson E10, E8 or 730 ultrasound machine equipped with a 2 – 4 MHz 4 D convex abdominal transducer. All scans were performed by the same operator (L.M.) in order to overcome inter-observer variability. The parameters were calculated off-line on recorded images to avoid discomfort for the patient and to minimize measurement biases that may arise from the lack of blindness of the operator to the patient subgroup.

The measurements were planned taking into account existing evidence on the effects of ACS on vascular parameters [19]. The baseline examination (E0) was performed before or within 4 hours of ACS administration (minimum 1 hour before ACS, maximum 4 hours after, mean 1 hour later), the first examination (E1) 24 – 48 hours and the second (E2) 7 days after the second dose of corticosteroids.

The measurements were normalized for gestational age using algorithms reported in the literature [11 – 13, 20, 21] and expressed as z-scores. Data were analyzed comparing the values before, shortly after and 1 week after treatment using pairwise comparisons with paired t-test with Holm's correction. Differences were considered to be significant as p-values were below 0.05. Statistical analysis was performed using SPSS version 23.0 (SPSS Inc, Chicago, IL, USA).

Results

26 AGA and 23 GR fetuses were initially enrolled in the study. Four fetuses (1 AGA and 3 GR fetuses) were excluded from the final analysis since they were delivered before the second examination could be performed. The analysis therefore includes 25 AGA and 20 GR fetuses with at least two examinations (E0-E1). Data on the third examination are available in 13 AGA and 11 GR fetuses. The remaining women were delivered within 7 days after the ACS course.

Patient characteristics are reported in ▶ **Table 1**. The two subgroups do not differ significantly for maternal characteristics, gestational age at enrolment and gestational age at delivery. Co-medications were administered to a significant proportion of both subgroups. Thirteen of the AGA pregnancies received tocolysis (atosiban) and 4 of the GR fetuses received anti-hypertensive drugs (methyldopa) for concomitant hypertensive disorders of pregnancy (HDP).

Mean baseline normalized values of vascular and cardiac indexes in the two populations are reported in ▶ **Table 2, 3**. The GR group showed significant peripheral and cardiac baseline abnormalities: an absent or reverse end diastolic flow (A/R EDF) in the UA that was present in 9 of 20 fetuses and a mean left MPI above the 95th percentile.

▶ **Table 4, 5** show the mean normalized values at E0, E1 and E2 for vascular and cardiac parameters for AGA and GR fetuses.

The feasibility of the measurements is reported as percentages in ▶ **Table 6**.

ACS restored UA-EDF in 6 of 9 GR fetuses with A/R-EDF ("return of end diastolic flow phenomenon") (▶ **Fig. 1**).

The results of pairwise comparisons (paired t-test with Holm's correction) between the 3 examinations are reported in ▶ **Table 7, 8**. In the AGA group ACS administration is associated with a significant reduction in UA PI (▶ **Fig. 2**). In the GR group, besides the reappearance of EDF, a significant worsening (increase) in the right MPI was recorded after ACS administration (E1-E2 and E0-E2) (▶ **Fig. 3**).

▶ **Table 1** Patient characteristics.

	AGA	GR	p
abdominal circumference percentile (Median, IQR)	50 (49.5 – 70)	3 (2.25 – 5)	0.000
maternal age (years) (Median, IQR)	31 (28.5 – 35.5)	30 (23 – 38.5)	0.529
nulliparity (n, %)	14, 56 %	15, 75 %	0.224
smoke (n, %)	5, 20 %	6, 30 %	0.729
BMI (Median, IQR)	24.45 (± 6.84)	21.50 (± 4.37)	0.198
comorbidity (n, %)	6, 24 %	2, 10 %	0.249
hypertensive disorders of pregnancy (n, %)	2, 8 %	5, 25 %	0.214
gestational age at first measurement (weeks) (median, IQR)	31 + 1 (26 + 5 – 33 + 1)	30 + 6 (27 + 1 – 32 + 1)	0.864
gestational age at delivery (weeks) (median, IQR)	34 + 0 (33 + 2 – 37 + 1)	32 + 4 (28 + 3 – 35 + 6)	0.175

▶ **Table 2** Mean normalized values of vascular parameters at E0 (1.65 = 95th percentile, –1.65 = 5th percentile).

	UA- A/R EDF (n)	UA PI	MCA PI	CPR	DV PI	RenA PI
AGA	0	0.01	– 0.74	– 0.24	– 0.32	– 0.37
GR	9	1.20	– 1.47	– 1.46	0.29	–0.92

▶ **Table 3** Mean normalized values of cardiac parameters at E0 (1.65 = 95th percentile, –1.65 = 5th percentile).

	Left MPI	Right MPI	Left E/A	Right E/A	MAPSE	TAPSE
AGA	1.47	1.08	– 0.86	– 0.33	– 1.12	– 0.43
GR	1.89	0.98	– 0.21	0.41	– 0.29	– 0.84

▶ **Table 4** Mean of normalized values at E0, E1 and E2 for vascular and cardiac parameters for AGA fetuses.

	E0	E1	E2
UA PI z-score (Mean, SD)	**0.008** (± 0.964)	**– 0.462** (± 1.004)	– 0.072 (± 1.011)
MCA PI z-score (Mean, SD)	– 0.737 (± 0.979)	– 0.805 (± 1.068)	– 0.189 (± 1.388)
CPR z-score (Mean, SD)	– 0.245 (± 1.406)	0.120 (± 1.629)	– 0.159 (± 0.770)
DV PI z-score (Mean, SD)	– 0.320 (± 1.179)	– 0.890 (± 0.975)	0.489 (± 1.459)
RenA PI z-score (Mean, SD)	– 0.368 (± 1.709)	– 0.669 (± 1.603)	– 0.556 (± 1.627)
left MPI z-score (Mean, SD)	1.469 (± 0.617)	1.693 (± 0.901)	1.625 (± 0.733)
right MPI z-score (Mean, SD)	1.084 (± 0.745)	1.020 (± 0.873)	1.187 (± 0.939)
left E/A z-score (Mean, SD)	– 0.861 (± 0.686)	– 0.377 (± 0.808)	– 0.381 (± 1.003)
right E/A z-score (Mean, SD)	– 0.332 (± 1.083)	– 0.383 (± 0.929)	0.264 (± 0.835)
MAPSE z-score (Mean, SD)	– 1.125 (± 1.472)	– 0.955 (± 1.836)	– 0.454 (± 1.809)
TAPSE z-score (Mean, SD)	– 0.432 (± 2.210)	– 0.397 (± 1.786)	0.335 (± 2.877)

▶ **Table 5** Mean (and SD) of normalized values at E0, E1 and E2 for vascular and cardiac parameters for GR fetuses.

	E0	E1	E2
UA PI z-score (Mean, SD)	1.204 (± 1.780)	1.139 (± 1.436)	1.298 (± 1.662)
MCA PI z-score (Mean, SD)	– 1.469 (± 1.396)	– 1.585 (± 1.166)	– 1.210 (± 1.038)
CPR z-score (Mean, SD)	– 1.468 (± 1.490)	– 1.401 (± 1.132)	– 1.056 (± 1.288)
DV PI z-score (Mean, SD)	0.293 (± 1.114)	0.110 (± 1.491)	0.037 (± 0.866)
RenA PI z-score (Mean, SD)	– 0.921 (± 1.071)	– 0.256 (± 1.232)	– 0.284 (± 1.682)
left MPI z-score (Mean, SD)	1.898 (± 0.948)	1.791 (± 0.713)	4.270 (± 3.834)
right MPI z-score (Mean, SD)	**0.985** (± 1.001)	**1.150** (± 0.776)	**3.551** (± 1.962)
left E/A z-score (Mean, SD)	– 0.208 (± 0.996)	0.315 (± 0.959)	0.352 (± 1.204)
right E/A z-score (Mean, SD)	0.409 (± 1.104)	– 0.009 (± 1.102)	– 0.168 (± 1.056)
MAPSE z-score (Mean, SD)	0.293 (± 3.745)	– 0.108 (± 5.207)	– 1.143 (± 1.639)
TAPSE z-score (Mean, SD)	– 0.840 (± 4.798)	– 0.632 (± 5.866)	– 1.725 (± 1.449)

▶ **Table 6** Feasibility of adequate measurements.

	%
UA PI	99
MCA PI	93
CPR	93
DV PI	84
left MPI	95
right MPI	89
left E/A	95
right E/A	95
MAPSE	91
TAPSE	94
RenA PI	85

▶ **Table 7** p-values of multiple comparisons for paired data in the 3 examinations in AGA fetuses.

	E0-E1	E1-E2	E0-E2
UA PI z-score	0.02*	0.22	0.25
MCA PI z-score	1	1	1
CPR z-score	0.20	0.11	0.31
DV PI z-score	0.45	0.17	0.13
RenA PI z-score	1	1	1
left MPI z-score	1	1	1
right MPI z-score	0.92	0.22	0.92
left E/A z-score	0.09	0.43	0.43
right E/A z-score	0.89	0.27	0.27
MAPSE z-score	1	1	1
TAPSE z-score	0.58	0.85	1

Discussion

This study shows that ACS administration produces hemodynamic changes in both AGA and GR fetuses, with more marked effects in the latter group. After corticosteroids administration, approximately two-thirds of GR fetuses show the previously described transient “return of EDF phenomenon”, whereas the AGA group shows a significant decrease in the UA PI shortly after betamethasone administration with normalization to the baseline by the third examination. Neither the MCA PIs nor the RenA PIs change after ACS in either of the two analyzed subgroups. Cardiac function deteriorates after corticosteroids in the GR group only, as suggested by a significant increase in the right MPI in the second and third examination.

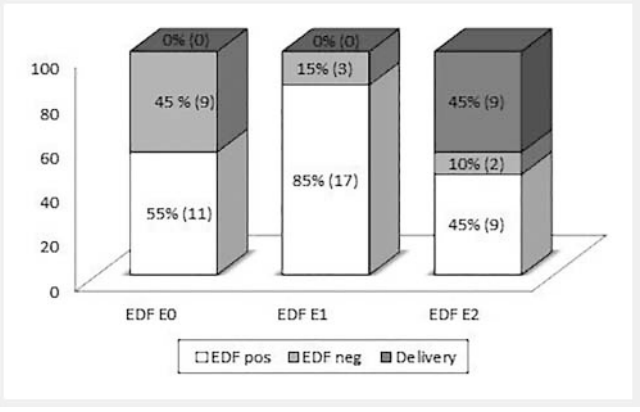
Hemodynamic effects of ACS on the feto-placental circulation have been extensively investigated over the last 2 decades, with conflicting results. One explanation may be that different models (humans and animals) with or without placental insufficiency were used in different settings (in vivo or in vitro) and different parameters were evaluated at various time intervals after the administration of either dexamethasone or betamethasone, that differ with respect to pharmacokinetics and effects [22].

In vitro studies have shown that corticosteroids produce vasodilation in both placental vessels [23] and the umbilical cord [24], although the precise mechanism (NO or not NO-mediated) remains elusive.

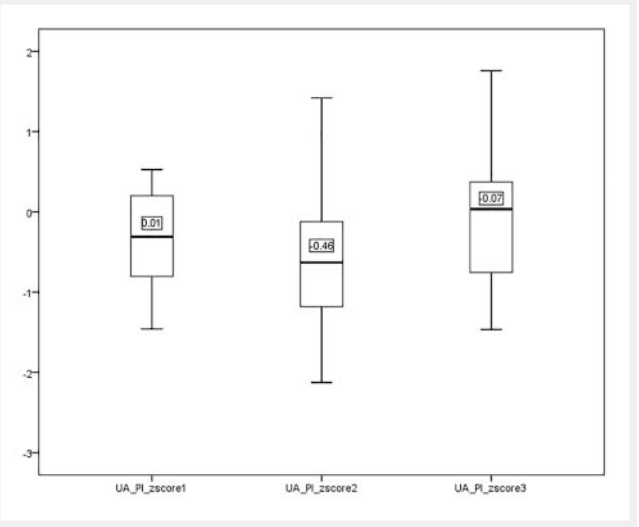
In vivo cardiovascular responses to ACS in healthy AGA animal fetuses (mainly sheep [25] and baboons [26]) point toward a vasoconstrictive effect with an increase in blood pressure, whereas the elegant studies of Miller and co-authors show the opposite effect in ovine models of GR, namely vasodilation in the feto-placental circulation [27, 28].

▶ **Table 8** p-values of multiple comparisons for paired data in the 3 examinations in GR fetuses.

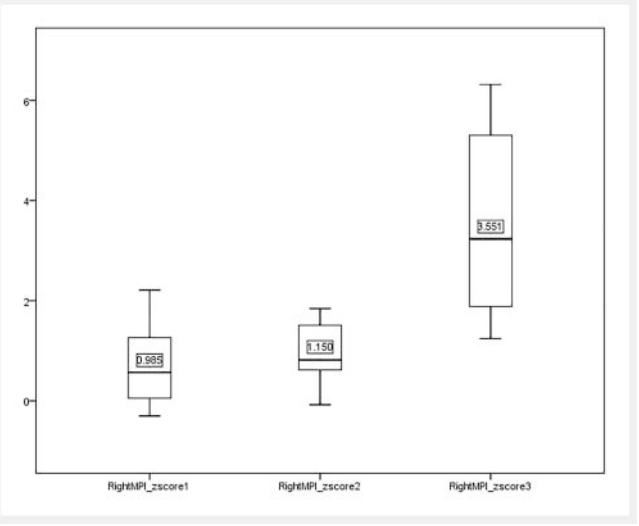
	E0-E1	E1-E2	E0-E2
UA PI z-score	0.79	0.05	0.10
MCA PI z-score	1	1	1
CPR z-score	1	1	1
DV PI z-score	0.48	0.17	0.98
RenA PI z-score	0.33	1	1
left MPI z-score	0.68	0.12	0.11
right MPI z-score	1	0.03*	0.04*
left E/A z-score	0.46	0.34	0.06
right E/A z-score	0.15	0.15	0.15
MAPSE z-score	1	1	1
TAPSE z-score	1	1	1



▶ **Fig. 1** Bar charts showing the percentages (and numbers) of A/R EDF, EDF and deliveries at times (E) 0, 1 and 2 in GR fetuses.



▶ **Fig. 2** Box and whisker plot of UA PI z-scores in the AGA at E0, E1 and E2.



▶ **Fig. 3** Box and whisker plot of right MPI z-scores in the GR group at E0, E1 and E2.

ACS were not proved to cause any significant effect on the UA Doppler of AGA human fetuses. This has also been confirmed by studies on monochorionic twin pregnancies with unequal sharing, in which ACS affected the sIUGR twin but had no effect on the AGA co-twin [29]. Other studies report a decrease in MCA PI in the AGA group after ACS administration [30]. A few pediatric studies published in the nineties showed that maternally administered corticosteroids decreased the need for blood pressure support in premature infants, thus pointing at a possible vasoconstrictive effect of these drugs on fetal circulation, irrespective of the presence or absence of placental insufficiency [31].

The concept of different effects exerted by corticosteroids on AGA and GR fetuses is well established in the literature and may be explained by a differential expression of placental enzymes or fetal corticosteroid receptors in normal and undernourished fetuses [32] or by changes in the regulation of vascular tone induced by placental insufficiency [3]. Besides, it has been shown by several studies that the effects of corticosteroids are tissue-type-dependent (e. g. vasodilating or vasoconstrictive depending on the vessel studied [2]).

In contrast to the literature [33], this study documents a decrease in UA PI in AGA fetuses, suggesting a vasodilator effect on placental vessels also in this group. We did not observe the previously reported decrease in MCA PI.

Our results confirm the ''return of end diastolic flow phenomenon'' in fetuses with placental dysfunction [19, 34 – 40], supporting the theory of a possible vasodilator effect of steroids on human placental or umbilical vessels. An inotropic effect of ACS on cardiac contractility may also be advocated as the other possible mechanism for the reappearance of end-diastolic velocities [41]. However animal studies seem to rule out this effect of corticosteroids [42].

Very few studies have been performed on cardiac response to ACS. In 2004 Kahler first included the measurement of peak systolic velocities (PSV) in the ductus arteriosus (DA) and in the pulmonary artery and the E/A ratios in the evaluation of 27 uneventful pregnancies that received ACS [8]. The PSV in the DA was shown to increase significantly. More recently functional echocardiography has been shown to be a useful instrument to reliably assess fetal cardiac function, enabling investigation of the adaptive cardiac response to placental insufficiency, a condition in which subclinical cardiac damage seems to be present already from the early stages of the disease [43]. In 2015, Pedersen and co-authors studied the MPIs and E/A ratios in 17 GR fetuses, showing a significant decrease in the right MPI after ACS and postulating an improvement due to corticosteroids in right cardiac function [9]. This result, however, may be influenced by the characteristics of the examined population, i. e. late GR (median GA 34^{+1} weeks, range 29^{+1}–37^{+4} weeks) with normal baseline parameters.

Our GR group, conversely, comprises fetuses with earlier diagnosis of placental insufficiency (median GA 30^{+6} weeks, range 27^{+1}–32^{+1} weeks) and with significant peripheral and cardiac hemodynamic abnormalities (altered UA and left MPI).

Our results show a worsening of right cardiac function after ACS administration and we postulate that cardiac overload due to vasodilation in the placental vessels may result in increased preload, negatively affecting the already challenged heart of GR fetuses. Similar effects were observed in the recipient fetus of twin-to-twin transfusion syndrome in monochorionic pregnancies and after intra-vascular transfusions that produce a similar status of increased pre-load [44]. Although worsening in right cardiac function one week after ACS may purely reflect the intrinsic deterioration of the fetal condition in placental insufficiency, the prompt increase in this parameter after administration (E1) supports a direct effect of the medication.

In this study both AGA and GR fetuses received other medications (atosiban and methyldopa) in conjunction with ACS. However, previous studies have shown no significant effects of these drugs on fetal hemodynamics [45, 46]. Moreover, in this study every fetus was used as its own control, thus minimizing the influence of co-medications on the results.

The strengths of this study are that we used normalized instead of raw values for the parameters investigated and the fact that all measurements were performed by the same operator [18]. The limitations are the relatively small sample size. However, it is arduous to obtain a complete 9-day data set in a cohort of fetuses with either threatened pre-term labor or severe GR, since the occurrence of spontaneous or iatrogenic delivery often prevents completion of the study protocol. The lack of a control group consisting of GR pregnancies not receiving ACS may be considered another limitation of the study. However, given the established clinical benefits of betamethasone in threatened preterm delivery, a placebo group would be considered unethical.

In conclusion, our data suggest that ACS cause vasodilation of placental vessels in both AGA and GR fetuses and the appearance of worsening in cardiac function, as inferred by an increase in the right MPI, in the latter group.

Conflict of Interest

The authors declare that they have no conflict of interest.

References

[1] Roberts D, Dalziel SR. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth (Review). The Cochrane Collaboration, The Cochrane Library. 2006. Issue 3

[2] Mulder EJH, de Heus R, Visser GHA. Antenatal corticosteroid therapy: short term effects on fetal behaviour and hemodynamics. Seminars in Fetal & Neonatal Medicine 2009; 14: 151 – 156

[3] Vidaeff AC, Blackwell SC. Potential risks and benefits of antenatal corticosteroid therapy prior to preterm birth in pregnancies complicated by severe fetal growth restriction. Obstet Gynecol Clin N Am 2011; 38: 205 – 2014

[4] Verburg BO, Jaddoe VWV, Wladimiroff JW et al. Fetal hemodynamic adaptative changes related to intrauterine growth- The generation R study. Circulation 2008; 117: 649 – 659

[5] Hodges RJ, Wallace EM. Mending a growth-restricted heart: should we use glucocorticoids? The Journal of Maternal-Fetal and Neonatal Medicine 2012; 25: 2149 – 2153

[6] Torrance HL, Derks JB, Scherjon SA et al. Is antenatal steroid treatment effective in preterm IUGR fetuses? Acta Obstetricia et Gynecologica 2009; 88: 1068 – 1073

[7] Van Meighem T, Hodges R, Jaeggi E et al. Functional echocardiography in the fetus with non-cardiac disease. Prenatal Diagnosis 2014; 34: 23 – 32

[8] Kahler C, Schleussner E, Müller A et al. Doppler measurements in feto-placental vessels after maternal betamethasone administration. Fetal Diagnosis and Therapy 2004; 19: 52 – 57

[9] Pedersen LH, Mogra R, Hyett J. The effects of corticosteroids on cardiac function in growth restricted fetuses; 2015. doi:10.1002/uog.15748

[10] ACOG Practice Bullettin, Number 134, May 2013.

[11] Parra-Cordero M, Lees C, Missfelder-Lobos H et al. Fetal arterial and venous Doppler pulsatility index and time averaged velocity ranges. Prenat Diagn 2007; 27: 1251 – 1257

[12] Baschat AA, Gembruch U. The cerebroplacental Doppler ratio revisited. Ultrasound Obstet Gynecol 2003; 21: 124 – 127

[13] Mari G, Abuhamad AZ, Uerpairojkit B et al. Blood flow velocity waveforms of abdominal arteries in appropriate and small for gestational age fetuses. Ultrasound Obstet Gynecol 1995; 6: 15 – 18

[14] Hernandez-Andrade E, Benavides-Serralde JA, Cruz-Martinez R et al. Evaluation of conventional Doppler fetal cardiac function parameters: E/A ratios, outflow tracts, and myocardial performance index. Fetal Diagn Ther 2012; 32: 22 – 29

[15] Messing B, Gilboa Y, Lipschuetz M et al. Fetal tricuspid annular plane systolic excursion (f-TAPSE):evaluation of fetal right heart systolic function with conventional M-mode ultrasound and spatiotemporal image correlation (STIC) M-mode. Ultrasound Obstet Gynecol 2013; 42: 182 – 188

[16] Hernandez-Andrade E, Lopez-Tenorio J, Figueroa-Diesel H et al. A modified myocardial performance (Tei) index based on the use of valve clicks improves reproducibility of fetal left cardiac function assessment. Ultrasound Obstet Gynecol 2005; 26: 227 – 232

[17] Crispi F, Gratacos E. Fetal Cardiac Function: Technical Considerations and Potential Research and Clinical Applications. Fetal Diagn Ther 2012; 32: 47 – 64

[18] Lobmaier SM, Cruz-Lemini M, Valenzuela-Alcaraz B et al. Influence of equipment and settings on myocardial performance index repeatability

and definition of settings to achieve optimal reproducibility. Ultrasound Obstet Gynecol 2014; 43: 632 – 639

[19] Edwards A, Baker LS, Wallace EM. Changes in feto-placental vessel flow velocity waveforms following maternal administration of betamethasone. Ultrasound Obstet Gynecol 2002; 20: 240 – 244

[20] Parasuraman R, Osmond C, Howe DT. Gestation-specific reference intervals for fetal cardiac Doppler indices from 12 to 40 weeks of gestation. Open Journal of Obstetrics and Gynecology 2013; 3: 97 – 104

[21] Gardiner HM, Pasquini L, Wolfenden J et al. Myocardial tissue Doppler and long axis function in the fetal heart. Int J Cardiol 2006; 113: 39 – 47

[22] Baud O, Sola A. Corticosteroids in perinatal medicine: How to improve outcomes without affecting the developing brain? Seminars in Fetal & Neonatal Medicine 2007; 12: 273 – 279

[23] Clifton VL, Wallace EM, Smith R. Short-term effects of glucocorticosteroids in the human fetal-placental circulation in vitro. J Clin Endocrinol Metab 2002; 87: 2838 – 2842

[24] Potter SM, Dennedy MC, Morrison JJ. Corticosteroids and fetal vasculature: effects of hydrocortisone, dexamethasone and betamethasone on human umbilical artery. BJOG 2002; 109: 1126 – 1131

[25] Schwab M, Roedel M, Anwar MA et al. Effects of betamethasone administration to the fetal sheep in late gestation on fetal cerebral blood flow. J Physiol 2000; 528: 619 – 632

[26] Koenen SV, Mecenas CA, Smith GS et al. Effects of maternal betamethasone administration on fetal and maternal blood pressure and heart rate in the baboon at 0.7 of gestation. Am J Obstet Gynecol 2002; 186: 812 – 817

[27] Miller LS, Chai M, Loose J et al. The effects of maternal betamethasone administration on the intrauterine growth-restricted fetus. Endocrinology 2007; 148: 1288 – 1295

[28] Miller SL, Supramaniam VG, Jenkin G et al. Cardiovascular responses to maternal betamethasone administration in the intrauterine growth-restricted ovine fetus. AJOG 2009; 201: 1 – 8

[29] Chang YL, Chang SD, Chao AS et al. Fetal hemodynamic changes following maternal betamethasone administration in monochorionic twin pregnancies featuring one twin with selective growth restriction and abnormal umbilical artery Doppler. J Obstet Gynaecol Res 2011; 37: 1671 – 1676

[30] Chitrit Y, Caubel P, Herrero R et al. Effects of maternal dexamethasone administration on fetal Doppler flow velocity waveforms. BJOG 2000; 107: 501 – 507

[31] Moïse AA, Wearden ME, Kozinetz CA et al. Antenatal steroids are associated with less need for blood pressure support in extremely premature infants. Pediatrics 1995; 95: 845 – 859

[32] Saif Z, Hodyl NA, Hobbs E et al. The human placenta expresses multiple glucocorticoid receptor isoforms that are altered by fetal sex, growth restriction and maternal asthma. Placenta 2014; 35: 260 – 268

[33] Cohlen BJ, Stigter RH, Derks JB et al. Absence of significant hemodynamic changes in the fetus following maternal betamethasone administration. Ultrasound Obstet Gynecol 1996; 8: 252 – 255

[34] Wallace EM, Baker L. Effect of antenatal betamethasone administration on placental vascular resistance. The Lancet 1999; 353: 1404 – 1407

[35] Müller T, Nanan R, Dietl J. Effect of antenatal corticosteroid administration on Doppler flow velocity parameters in pregnancies with absent or reverse end-diastolic flow in the umbilical artery. Acta Obstet Gynecol Scand 2003; 82: 794 – 796

[36] Simchen MJ, Alkazaleh F, Adamson SL et al. The fetal cardiovascular response to antenatal steroids in severe early-onset intrauterine growth restriction. AJOG 2004; 190: 296 – 304

[37] Wijnberger LD, Bilardo CM, Hecher K et al. Effect of antenatal glucocorticoid therapy on arterial and venous blood flow velocity waveforms in severely growth-restricted fetuses. Ultrasound Obstet Gynecol 2004; 23: 584 – 589

[38] Nozaki AM, Francisco RP, Fonseca ES et al. Fetal hemodynamic changes following maternal betamethasone administration in pregnancies with fetal growth restriction and absent end-diastolic flow in the umbilical artery. Acta Obstetricia et Gynecologica 2009; 88: 350 – 354

[39] Thuring A, Malcus P, Maršál K. Effect of maternal betamethasone on fetal and uteroplacental blood flow velocity waveforms. Ultrasound Obstet Gynecol 2011; 37: 668 – 672

[40] Piazze J, Dillon KC, Cerekja A. Betamethasone effects on umbilical arteries and ductus venosus Doppler velocity waveforms in growth-restricted fetuses. J Matern Fetal Neonatal Med 2012; 25: 1179 – 1182

[41] Lee Adamson S. Arterial pressure, vascular input impedance and resistance as determinants of pulsatile flow in the umbilical artery. European Journal of Obstetrics and Gynecology and Reproductive Biology 1999; 84: 119 – 125

[42] Tare M, Miller SL, Wallace EM et al. Glucocorticoid treatment does not alter early cardiac adaptations to growth restriction in preterm sheep fetuses. BJOG 2012; 119: 906 – 914

[43] Crispi F, Hernandez-Andrade E, Pelsers MMAL et al. Cardiac dysfunction and cell damage across clinical stages of severity in growth restricted fetuses. Am J Obstet Gynecol 2008; 199: 254.e1 – 254.e8

[44] Sikkel E, Klumper FJCM, Oepkes D et al. Fetal cardiac contractility before and after intrauterine transfusion. Ultrasound Obstet Gynecol 2005; 26: 611 – 617

[45] Grzesiak M, Wilczynski J. Preliminary report of 48-hours Atosiban administration in spontaneous preterm labour- Doppler blood flow assessment of placental and fetal circulation. Neuro Endocrinol Lett 2013; 34: 681 – 686

[46] Günenc H, Cicek N, Gorkemli H et al. The effect of methyldopa treatment on uterine, umbilical and middle cerebral artery blood flow in pre-eclamptic patients. Arch Gynecol Obstet 2002; 266: 141 – 144