Received: 7 December 2023 | Revised: 26 February 2024 | Accepted: 10 March 2024

DOI: 10.1002/ijgo.15491

CLINICAL ARTICLE

Obstetrics

Anatomical and functional changes of the fetal adrenal gland in intrauterine growth restriction

Serena Martinelli[1,2,3] | Alessandro Rolfo[4] | Carlotta Pace[5] | Letizia Canu[1,2,3] | Anna Maria Nuzzo[4] | Domenica Giuffrida[4] | Pietro Gaglioti[5] | Tullia Todros[4,5]

[1]Department of Experimental and Clinical Biomedical Sciences "Mario Serio", University of Florence, Florence, Italy

[2]Centro di Ricerca e Innovazione sulle Patologie Surrenaliche, AOU Careggi, Florence, Italy

[3]European Network for the Study of Adrenal Tumors, (ENS@T) Center of Excellence, Florence, Italy

[4]Department of Surgical Sciences, University of Turin, Turin, Italy

[5]AOU Città della Salute e della Scienza, Sant' Anna Hospital, Turin, Italy

Correspondence
Serena Martinelli, Department of Experimental and Clinical Biomedical Sciences "Mario Serio", University of Florence, Viale Pieraccini 6, 50139 Florence, Italy.
Email: serena.martinelli@unifi.it

Funding information
Università degli Studi di Torino

Abstract

Objective: The aim of this study was to demonstrate the establishment of adrenal sparing in intrauterine growth restricted (IUGR) human fetuses. IUGR fetuses are a subgroup of small for gestational age (SGA) fetuses that are unable to reach their own growth potential because of chronic hypoxia and undernutrition. We hypothesized that in IUGR fetuses the adrenal gland is relatively larger and secretion of noradrenaline (NA), adrenaline (A), and cortisol is increased.

Study Design: This is a prospective observational study including 65 singleton pregnancies (42 IUGR and 23 controls). Using two-dimensional ultrasound, we measured fetal adrenal diameters and adrenal/abdominal circumference (AD/AC) ratio between 25 and 37 weeks. We considered only one measurement per fetus. In 21 pregnancies we also measured NA, A, and cortisol levels in arterial and venous fetal cord blood collected at the time of delivery.

Results: The AD/AC ratio was significantly higher in IUGR fetuses than in controls. Cord NA and A levels were significantly higher in IUGR fetuses than in controls. An increase in cortisol secretion in IUGR fetuses was observed but the difference was not statistically significant.

Conclusions: Adrenal sparing correlates with a relative increase in adrenal measurements and function.

KEYWORDS
adrenal gland, adrenaline, cortisol, human fetus, intrauterine growth restriction, noradrenaline, prenatal ultrasound

1 | INTRODUCTION

Small for gestational age (SGA) fetuses are defined by an estimated fetal weight or ultrasound measurement of abdominal circumference (AC) below the 10th percentile. SGA includes both constitutionally small but otherwise healthy fetuses and fetuses who have failed to reach their genetically determined growth potential, because of chronic hypoxia and undernutrition.[1] The latter are defined as intrauterine growth restricted (IUGR).[2–4]

Intrauterine growth restriction remains a challenging problem, especially in developing countries where it affects almost 30 million infants each year[5] and is associated with significant neonatal mortality and morbidity, and it carries potential long-term complications throughout life.[3,5–7] IUGR fetuses develop in a chronic hypoxic and hypoglycemic environment.

Distinguishing between constitutional SGA and IUGR fetuses can be challenging because they both involve fetal measurements below the expected norms. However, various prenatal imaging

techniques such as ultrasound and Doppler ultrasound, coupled with a comprehensive assessment of clinical evaluation, maternal history, and laboratory tests, can allow the correct differential diagnosis.[8]

The fetal adaptive response to the adverse environmental condition has been studied in animal models and is based on redistribution of blood flow, meant to favor the growth and function of brain, heart, and adrenal glands to the detriment of other districts (mainly renal and splanchnic districts).[7,9,10] As adrenals play a crucial role in producing hormones essential for several bodily functions, the concept of adrenal sparing refers to preservation of the adrenal gland function to maintain hormone secretion and to prevent complications associated with adrenal insufficiency. Studies on animal models suggest that adrenal sparing in IUGR is related to an enhancement of cortisol and catecholamine synthesis, aimed at supporting fetal adaptation to chronic hypoxia and hypoglycemia.[11,12]

When ultrasound and Doppler ultrasound became available, it became possible to study adrenal size and blood flows in the human fetus throughout normal and complicated pregnancies.[13–17] Some biometric and Doppler studies comparing adrenal size or adrenal blood flow in normal and IUGR fetuses confirm the adrenal sparing effect[18–21] while others do not.[22,23] The different results obtained in these studies are most likely due to heterogeneity of the SGA populations as adrenal sparing is expected to be present in the IUGR subgroup, which represents only a proportion of all SGA fetuses.

To our knowledge, there are no studies investigating the morphological and functional changes of the adrenal gland related to IUGR in humans.

The main aim of the present study was to demonstrate the establishment of adrenal sparing in IUGR fetuses, investigating both morphological and functional aspects.

Particular attention has been paid to the identification of IUGR fetuses considering their growth pattern and maternal and feto-placental Doppler velocimetry. We hypothesized that adrenal sparing contributes to maintaining, or even increasing, fetal adrenal gland size, combined with a functional arousal of the gland, with enhanced synthesis of catecholamines and cortisol.

2 | MATERIALS AND METHODS

A prospective observational study was conducted from January 2014 to May 2017 at Obstetrics and Gynecology 2U Department of Sant' Anna University Hospital in Turin, Italy.

The study protocol was approved by local ethics committee (ethics review committee no. 100364/A210).

Inclusion criteria were singleton pregnancy, certain gestational age (GA) (assessed at first trimester ultrasound), and GA above 25 weeks at recruitment. Exclusion criteria were fetal structural or genetic anomalies, pregestational maternal hypertension, or other pregestational maternal conditions which could affect fetal growth, documented fetal, or maternal infections.

Fetuses matching inclusion criteria were recruited and categorized into two groups: IUGR and controls (appropriate for GA fetuses, born at term after an uneventful pregnancy). After informed consent, the assignment to study group was based on fetal growth evaluation through ultrasound biometry and fetal and/or maternal Doppler velocimetry.

IUGR was considered in the presence of one of the following:

- AC <10th centile for GA[24] with pathological uterine artery Doppler velocimetry and/or pathological umbilical artery Doppler velocimetry.
- AC ≥10th centile but growth trajectory down-crossing centiles >2 quartiles on growth charts[24] with pathological uterine artery Doppler velocimetry and/or pathological umbilical artery Doppler velocimetry.

Uterine artery Doppler velocimetry was defined as pathological in the presence of a mean pulsatility index above 95th centile for GA, according to pulsatility index charts by Gòmez et al.[25]

Fetal umbilical artery Doppler velocimetry was defined as pathological in the presence of pulsatility index above 60th centile for GA, according to pulsatility index charts by Todros et al.[26] These charts result from an Italian multicenter study carried out in a high-risk population, which demonstrated that the 60th centile curve is the most sensitive cut-off to identify fetuses at risk of hypoxia.

For all included cases we collected data about delivery and short-term neonatal follow-up. Adverse neonatal outcome was defined by the presence of at least one of the following: neonatal intensive care unit (NICU) stay >30 days, grade 3 to 4 intraventricular hemorrhage, bronchopulmonary dysplasia, necrotizing enterocolitis, grade 3–5 retinopathy of prematurity, and neonatal death.

2.1 | Morphological study

All recruited fetuses underwent standard biometric measurements (head circumference, AC, femur length). Then, the fetal kidney proximal to the probe was identified on a sagittal plane and the adrenal gland was visualized cranial to the kidney.

Through slight rotation of the probe, the plane comprising the largest diameter of the adrenal gland was obtained and two measurements recorded: (1) the antero-posterior, the largest diameter (Figure 1, D1); and (2) the cranio-caudal, the maximal thickness (Figure 1, D2). The calipers were placed directly at the interface between the gland and the surrounding soft tissues and, on one side, at the interface with the kidney.

The mean adrenal diameter (AD) for each fetus was calculated as: (cranio-caudal diameter + antero-posterior diameter)/2.

As the AC is the ultrasound parameter that best reflects fetal size, the mean adrenal diameter/abdominal circumference (AD/AC) ratio for each fetus was calculated with the purpose of correcting for different fetal size. Moreover, the ratio is independent of GA.

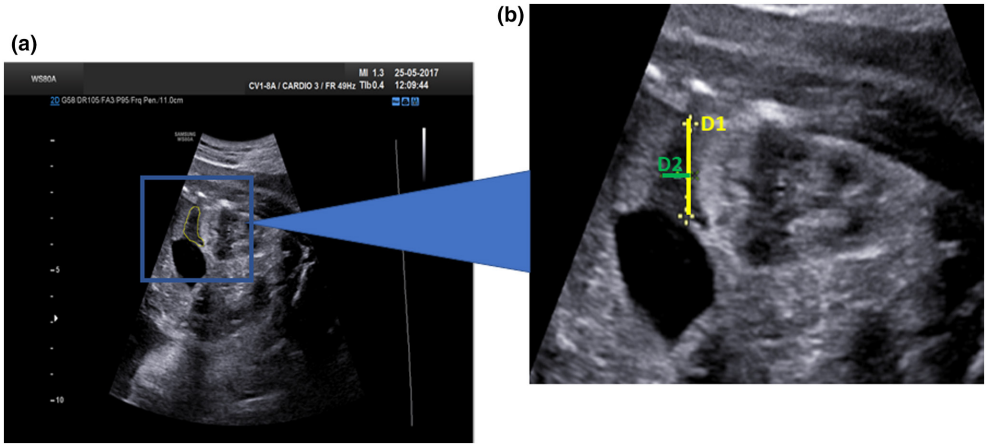

FIGURE 1 (a) Identification of fetal adrenal gland on a parasagittal plan; and (b) enlargement showing the measurement of craniocaudal (D1) and antero-posterior diameter (D2).

For each case, only the measurements obtained at recruitment were used.

Ultrasound measurements were accomplished by a single senior sonographer, using the Voluson 730 Expert (General Electric, Fairfield, CT, USA) equipped with a 5.0–7.0 MHz transabdominal probe.

2.2 | Functional study

A subgroup of recruited cases was included in the functional study of the fetal adrenal gland, which involved measuring noradrenaline (NA), adrenaline (A), and cortisol in the arterial and venous blood of the umbilical cord, at time of birth. Fetuses were considered eligible for the functional study only if they were delivered by elective cesarean section (CS) without labor, so as to avoid the confounding effect of labor itself on maternal and fetal adrenergic activity. Ethical issues prevented us from considering antenatal cord blood sampling instead of cord blood sampling at the time of delivery.

We excluded all cases for which blood sample collection at delivery was not possible due to technical problems. In this respect, it is important to stress the technical difficulty in collecting cord blood samples, especially in IUGR fetuses, due to the small size of the fetal cord with a tendency to rapid intra-cord blood coagulation at delivery. We also excluded patients treated with betamethasone for respiratory distress syndrome (RDS) prophylaxis in the 7 days before delivery, to avoid the effect that an exogenous steroid might confer.

We collected fetal arterial and venous cord blood samples after double cord-clamping, performed immediately after delivery directly on the operating field. Samples were collected in lithium-heparin test tubes. All samples were stored at 4°C for a maximum of 6 h, and then centrifuged at 6000 rpm for 3 min; separated serum was stored at −20°C until analysis at Baldi e Riberi Analysis Laboratory (Città della Salute e della Scienza, Turin, Italy). NA and A were measured by high-performance liquid choromatography (HPLC) analysis (catecholamines in plasma – HPLC kit; Chromosystems, Becton Dickinson, New Jersey, USA). Cortisol was measured by ECLIA (Elettro Chemiluminescence Immuno Assay) using the (Cobas kit for Elecsys, Roche, Basel, Swizerland) immunoanalyzers.

2.3 | Statistical analysis

Data are presented as median (range) for continuous variables and as *n* (%) for categorical variables. Groups were compared using Mann–Whitney test with significance level $P<0.05$. The analyses were performed using the statistical software package GraphPad Prism Version 8.3.0.

3 | RESULTS

3.1 | Morphological study

A total of 65 fetuses were included: IUGR ($n=42$), controls ($n=23$). The characteristics of the two groups are reported in Table 1. Maternal age and parity were similar in the two groups. Most IUGR fetuses received corticosteroids for RDS prophylaxis, while only a few received $MgSO_4$ for neuroprotection. As expected, maternal and/or fetal complications led to high CS rates (up to 90%) in the IUGR group. The quite high CS rate (56.5%) and RDS prophylaxis rate (30.4%) in controls, despite the absence of IUGR, can be explained by a selection bias: we preferentially included women expected to undergo elective CS (fetal breech presentation, placenta previa, previous CS) to be able to perform cord blood samples for the functional study without affecting the levels of catecholamines. Indeed, if spontaneous delivery occurred, massive catecholamine secretion would be recorded. According to our local protocols, RDS prophylaxis was administered to all women undergoing elective CS before 39 weeks. Fetal gender distribution was similar in the two groups. GA at birth and birth weight (BW) were significantly lower in the IUGR group compared with controls

TABLE 1 Obstetric and neonatal characteristics for each study group (morphological study). Groups were compared as follows: intrauterine growth restricted (IUGR) versus controls (Mann–Whitney; significance level: $P<0.05$).

	IUGR ($n=16$)	Controls ($n=23$)	$P<0.05$
Maternal age (year) (median [range])	34 (19–43)	34 (19–44)	-
Nulliparity (%)	67	48	-
GA at recruitment (week) (median [range])	30 (23–38)	33 (26–39)	$P<0.001$
RDS prophylaxis (%)	98	30	$P<0.001$
$MgSO_4$ prophylaxis (%)	16	0	$P<0.05$
Cesarean section (%)	97	56	$P<0.001$
GA at birth (week) (median [range])	32 (28–38)	38 (33–41)	$P<0.0001$
Female gender (%)	46	52	-
Birth weight (g) (median [range])	1245 (570–2440)	3190 (2110–4300)	$P<0.0001$
Birth weight centile (median [range])	6° (0°–25°)	56° (15°–99°)	$P<0.0001$
Composite adverse neonatal outcome (%)	51%	0%	-

Note: Composite adverse neonatal outcome was defined by the presence of at least one of the following: neonatal intensive care unit stay >30 days, grade 3–4 intraventricular hemorrhage, bronchopulmonary dysplasia, necrotizing enterocolitis, grade 3–5 retinopathy of prematurity, neonatal death.
Abbreviations: GA, gestational age; RDS, respiratory distress syndrome.

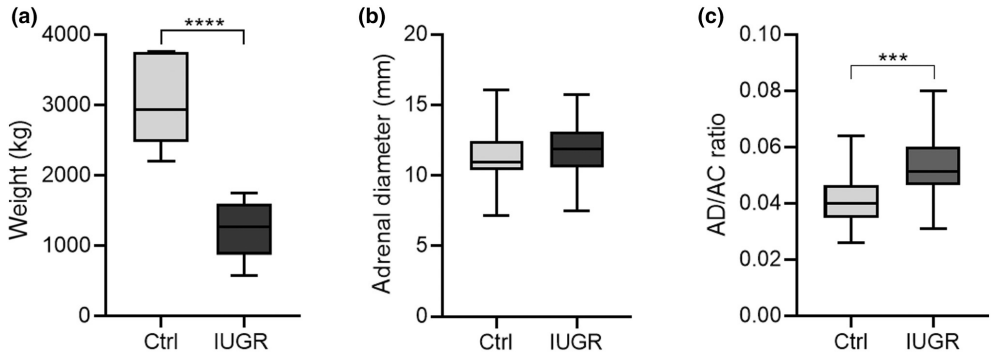

FIGURE 2 Morphological study. (a) Weight differences between control and intrauterine growth restricted (IUGR) groups; (b) adrenal mean diameters of control and IUGR groups; (c) differences in the adrenal/abdominal circumference (AD/AC) ratio among groups (IUGR, $n=42$; controls, $n=23$) ****$P<0.00001$; *** $P<0.001$. Ctrl, control.

(Table 1). No differences were noticed among groups in the rate of low Apgar scores at 5 min. As expected, the mean IUGR BW was significantly lower compared with controls (IUGR: 1237 g [570–1750]; controls: 3023 g [2200–3760]; IUGR vs controls: $P<0.0001$) (Figure 2a). Mean adrenal diameter was not significantly different between groups: (IUGR: 11.78 mm [7.45–15.7]; controls: 11.26 mm [7.15–16.05]; IUGR vs controls: $P=0.158$) (Figure 2b). However, the mean GA at entry was significantly lower in the IUGR group (30 vs 33 weeks; Table 1). In stark contrast, median AD/AC ratio was significantly greater in the IUGR group compared with controls, (IUGR: 0.053 [0.031–0.08]; controls: 0.041 [0.026–0.064]; IUGR vs controls: $P<0.0001$) (Figure 2c). The ratio was not different between male and female fetuses in both IUGR and controls (data not shown). Scatterplots indicate that the adrenal mean diameter grew throughout pregnancy, in both normal and IUGR fetuses, with IUGR AD always larger than the AD of control fetuses (Figure 3a). The AD/AC ratio decreased throughout normal pregnancy. In IUGR fetuses, the decrease was steeper due to much higher values at lower GA (Figure 3b).

3.2 | Functional study

A total of 21 fetuses were included: IUGR ($n=15$), controls ($n=6$). The characteristics of the two groups are reported in Table 2.

Only pregnancies delivered by elective CS were included in the functional study. Maternal age and parity were similar in the two groups. Corticosteroid prophylaxis was administered in all IUGR fetuses and in 66.6% of control fetuses. Fetal gender distribution was similar. GA at birth and BW were significantly lower in the IUGR group than in controls (Table 2). No differences were noticed between groups in the rate of low Apgar scores at 5 min.

As in the morphological study, mean AD was not significantly different between the two groups (IUGR: 12.36 mm [9.35–15.30]; controls: 11.73 mm [9.45–15.30]; IUGR vs controls: $P=0.235$), while the median AD/AC ratio was significantly higher in IUGR fetuses compared with controls (IUGR: 0.055 [0.046–0.072]; controls: 0.038 [0.029–0.045]; IUGR vs controls: $P<0.0001$).

We observed significantly higher NA levels in both arterial and venous cord blood of IUGR group compared with controls (arterial, IUGR:

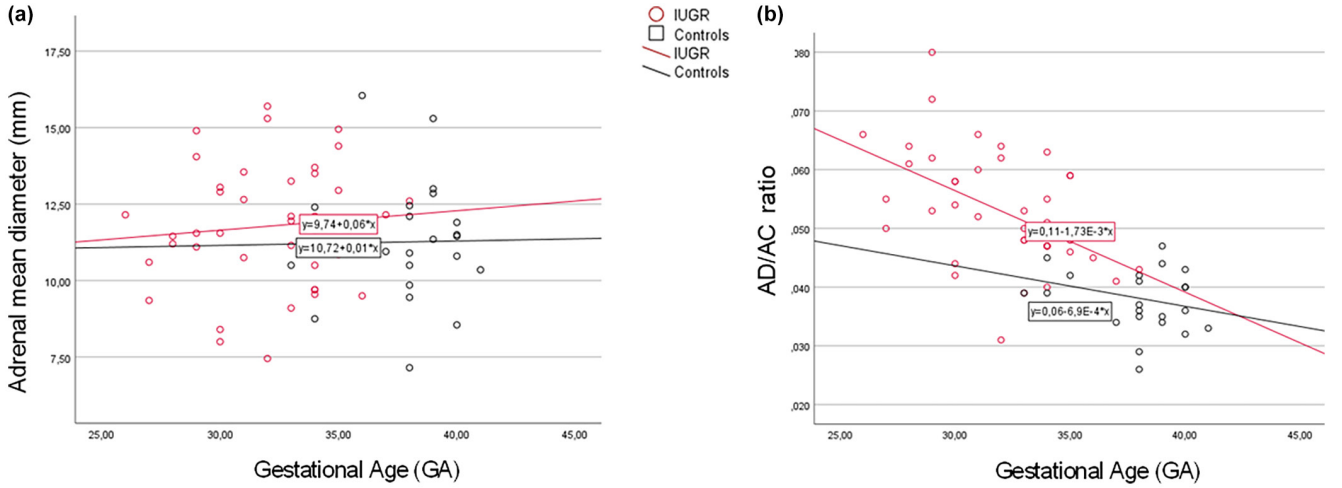

FIGURE 3 Scatterplots indicate the relationship between gestational age and adrenal diameters (a) and adrenal/abdominal circumference (AD/AC) ratio (b) in controls and intrauterine growth restricted (IUGR) fetuses.

TABLE 2 Obstetric and neonatal characteristics for each study group (functional study). Groups were compared as follows: intrauterine growth restricted (IUGR) versus controls (Mann–Whitney; significance level: $P<0.05$).

	IUGR ($n=12$)	Controls ($n=6$)	$P<0.05$
Maternal age (year) (median [range])	35 (19–43)	37.5 (25–44)	-
Nulliparity (%)	75	33.4	-
GA at recruitment (week) (median [range])	29 (26–31)	36.5 (30–39)	$P<0.001$
RDS prophylaxis (%)	100	66.6	-
MgSO4 prophylaxis (%)	8.3	0	-
Cesarean section (%)	100	100	-
GA at birth (week) (median [range])	31.75 (27–35)	37.5 (34–39)	$P<0.001$
Female gender (%)	45.4	33.4	-
Birth weight (g) (median [range])	1226 (570–1750)	2935 (2200–3760)	$P<0.001$ $P=0.004$
Birth weight centile (median [range])	3° (1°–5°)	52.5° (25°–88°)	$P<0.001$ $P=0.004$

Note: Composite adverse neonatal outcome was defined by the presence of at least one of the following: neonatal intensive care unit stay >30 days, grade 3–4 intraventricular hemorrhage, bronchopulmonary dysplasia, necrotizing enterocolitis, grade 3–5 retinopathy of prematurity, neonatal death.
Abbreviations: GA, gestational age; RDS, respiratory distress syndrome.

3482 pg/mL [1030–6500]; controls: 951.7 [440–1950]; IUGR vs controls: $P=0.014$; venous, IUGR: 1409 pg/mL [370–3800]; controls: 408.5 [10–983]; IUGR vs controls: $P=0.031$); (Figure 4a). NA was also higher in arterial cord blood compared with venous cord blood samples in both IUGR and controls (IUGR, $P=0.006$; controls, $P=0.039$) (Figure 4a).

With regard to A measurements, more than half of the values were below threshold levels. Despite this, we observed significantly higher values in IUGR compared with controls in both venous and arterial samples (arterial, IUGR: 187.5 pg/mL [175–200]; controls, 73 [31–148]; IUGR vs controls: $P=0.052$; venous, IUGR: 275.3 pg/mL [220–340]; controls, 10 [9.8–10.2]; IUGR vs controls: $P=0.005$); (Figure 4b). We did not observe any difference between arterial and venous A levels within the IUGR group or within the controls (Figure 4b).

Cortisol blood levels showed a trend towards higher arterial and venous levels in IUGR compared with controls (arterial, IUGR: 21.65 µg/dL [2.4–73.4]; controls: 18.90 µg/dL [3.5–39.90]; IUGR vs controls: $P=0.453$; venous, IUGR: 13.88 µg/dL [0.3–56.7]; controls, 10.86 µg/dL [0.4–33.6]; IUGR vs controls: $P=0.371$); (Figure 4c). There were no significant differences between arterial and venous levels in both IUGR fetuses and controls (Figure 4c).

Interestingly, the arterial NA of the IUGR group was significantly higher in male fetuses than in female fetuses (data not shown); however, the number of cases in each group was too small to allow meaningful speculations.

4 | DISCUSSION

In the present study, we report, for the first time to our knowledge, the adrenal-sparing effect in human IUGR fetuses associated with changes in adrenal hormones.

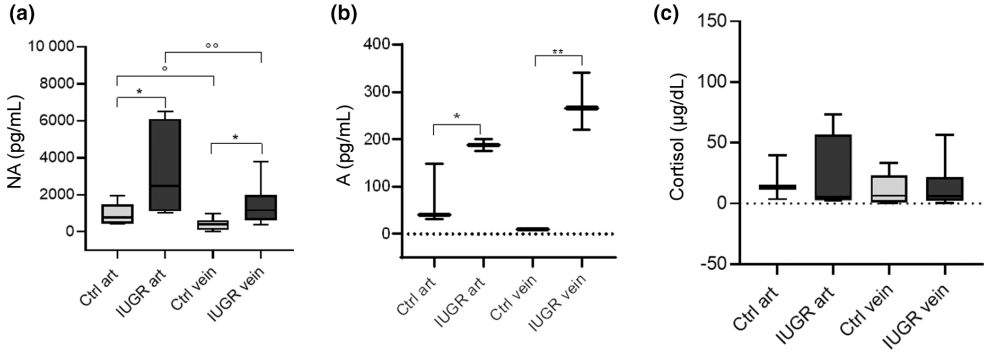

FIGURE 4 Functional study. (a–c) Noradrenaline (a), adrenaline (b), and cortisol (c) levels in fetal cord venous and arterial blood samples (*$P < 0.05$; **$P < 0.01$; °°$P < 0.01$; °$P < 0.05$). art, artery; Ctrl, control; IUGR, intrauterine growth restricted.

We observed higher AD/AC ratio in IUGR fetuses than in controls, showing that the IUGR adrenal gland is larger than expected based on fetal size. Interestingly, the difference was increasingly larger at decreasing GA, indicating that the degree of adrenal sparing is related to the severity of the disease, since early onset IUGR are usually the most severe cases (Figure 3b). The absolute value of AD was slightly larger in IUGR than in controls despite the significantly lower GA of the IUGR group (Figure 3a). Also, we found significantly higher levels of NA in IUGR arterial and venous samples compared with controls. NA levels were higher in the artery than in the vein, in both IUGR fetuses and controls, suggesting the fetal origin of NA. Also, A values were significantly higher in IUGR fetuses, but without any difference between artery and vein in both IUGR fetuses and controls. The same was true for cortisol levels, although the difference between IUGR fetuses and controls did not reach statistical significance, probably due to the small sample size.

Recently, other studies have demonstrated relative larger adrenal size in SGA and/or IUGR fetuses.[19–21] The main aim of these studies was to find new ultrasound parameters able to predict fetal outcome. Instead, we wanted to investigate the pathophysiology of IUGR in the human fetus. Therefore, we used very strict biometric and Doppler velocimetry criteria in order to select genuine IUGR fetuses—avoiding including small but otherwise normal fetuses—and extended the study to measurement of the levels of the adrenal hormones in the umbilical cord at birth.

In an animal model of chronic hypoxia, Poudel et al.[27] found an increase of blood flow and of oxygen and glucose delivery to the adrenal gland; they also found that the fetal adrenal gland absolute weight was lower compared with control animals, but the adrenal weight relative to BW was higher in accordance with our findings. Thus, it can be assumed that hypoxemia induces redistribution of blood flows with preferential flow to the adrenal gland that maintains normal, or nearly normal, growth. However, this model does not satisfactorily explain the increased hormone secretion. Another more plausible explanation is that hypoxemia directly impacts on the pituitary–adrenal axis, inducing the increase of cortisol secretion and on the sympatho-adrenal system, as has been shown in animal models.[28,29] Therefore, the larger adrenal measurements found in our study could also be explained by an increase in its function (Figure 5).

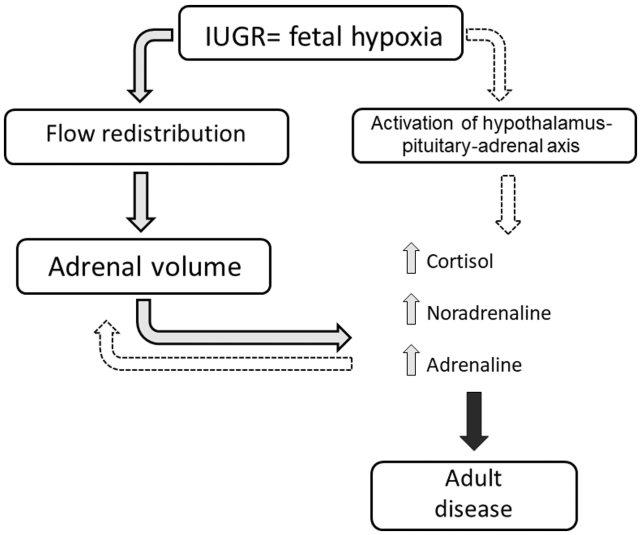

FIGURE 5 Adrenal sparing: two possible explanations. (1) Fetal hypoxia induces blood flow redistribution to the advantage of brain, heart, and adrenal glands; the increase in blood flow supports the growth and function of the adrenals that produce a larger amount of hormones compared with normal fetuses. (2) Fetal hypoxia triggers the activation of the hypothalamic–pituitary–adrenal axis, which in turn stimulates the adrenal function and hence increases hormone secretion and results in larger adrenal size compared with normal fetuses.

The key roles of NA and A in fetal homeostasis are well known. NA and A are catecholamines that act as both stress hormones and neurotransmitters. A inhibits fetal insulin secretion by acting on alpha-2-adrenergic receptors on pancreatic beta-cells. This down-regulation of insulin secretion is aimed at maintaining catabolic disposition, which is essential under conditions of nutrient deficiency such as IUGR. Adrenal activation in growth-restricted fetuses is an effective adaptive response to chronic hypoxia and hypoglycemia, but also leads to chronic fetal catecholamine overexposure and possibly to long-term detrimental effects. NA and A in the blood vessels trigger vasoconstriction, which increases blood pressure.

Regarding the developmental origins of hypertension, multiple downstream mechanisms have been described, including vascular alterations and hyperactivity of the hypothalamic–pituitary–adrenal axis.[30,31] In animals, several models have been used to investigate the effects of perturbations to the fetal environment on subsequent hypertensive disease. IUGR rat models show endothelial dysfunction and follow-up of these new-born rats showed an adult phenotype characterized by exercise-induced sympathetic over-activation and hypertension.[32,33] Bibeau et al.[12] reported that alterations in adrenal steroidogenesis and catecholamine synthesis in rat IUGR fetuses were associated with the presence of hypoxia, oxidative stress, and the induction of genes involved in inflammation induction. In humans, Lurbe et al.[34] demonstrated an increase in blood pressure (BP) during the first month of life, and persistence of relatively elevated BP at the end of the first year, indicating that children born with low birthweight were prone to develop a phenotype that may lead to a progressive increment of BP over time. Yadav et al.[35] reported significant positive associations between increased BP in young adulthood and several fetal growth parameters, such as abdominal and head circumference, using trajectory modeling based on serial ultrasound measures during pregnancy.

More recently, systematic reviews and meta-analyses have confirmed the inverse association between lower BW and higher BP in later life, across age groups and independent of body mass index.[35–38]

This is the first study taking into consideration both morphological and functional parameters of the adrenal glands in human IUGR fetuses. Unfortunately, the number of fetuses studied was too small to draw solid conclusions and we still lack a long-term follow-up of the IUGR fetuses recruited into this study.

5 | CONCLUSION

In conclusion, our work, for the first time, shows in the human fetus morphological and functional alterations of the adrenal gland that may explain the origin of some adult diseases.

AUTHOR CONTRIBUTIONS

Design of the work: CP, TT. *Contributions to the conception*: TT, AR, DG. *Interpretation of data for the work*: SM, LC, PG, AMN. *Drafting the work*: TT, DG, CP, SM. *Reviewing the work*: AR, LC, PG, AMN. *Final approval*: TT, DG, CP, SM, AR, LC, PG, AMN. *Agreement to be accountable for all aspects of the work*: TT, DG, CP, SM, AR, LC, PG, AMN.

FUNDING INFORMATION

This study was funded by the University of Turin in 2012. Samples were collected between 2013 and 2017, after which the analyses were carried out.

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available.

ORCID

Serena Martinelli https://orcid.org/0000-0003-4992-2252

REFERENCES

1. Robinson JS, Moore VM, Owens JA, McMillen IC. Origins of fetal growth restriction. *Eur J Obstet Gynecol Reprod Biol*. 2000;92(1):13-19.
2. Khadilkar AV, Parthasarathy LS. Fetal growth restriction and cardiovascular health among adolescents. *Indian Pediatr*. 2015;52(2):107-108.
3. McMillen IC, Adams MB, Ross JT, et al. Fetal growth restriction: adaptations and consequences. *Reproduction*. 2001;122(2):195-204.
4. ACOG Practice bulletin no. 134: fetal growth restriction. *Obstet Gynecol*. 2013;121(5):1122-1133.
5. Imdad A, Yakoob MY, Siddiqui S, Bhutta ZA. Screening and triage of intrauterine growth restriction (IUGR) in general population and high risk pregnancies: a systematic review with a focus on reduction of IUGR related stillbirths. *BMC Public Health*. 2011;11(Suppl 3):S1.
6. Alison M, Biran V, Tanase A, et al. Quantitative shear-wave elastography of the liver in preterm neonates with intra-uterine growth restriction. *PLoS One*. 2015;10(11):e0143220.
7. Unterscheider J, O'Donoghue K, Daly S, et al. Fetal growth restriction and the risk of perinatal mortality-case studies from the multicentre PORTO study. *BMC Pregnancy Childbirth*. 2014;14:63.
8. Lees CC, Stampalija T, Baschat A, et al. ISUOG practice guidelines: diagnosis and management of small-for-gestational-age fetus and fetal growth restriction. *Ultrasound Obstet Gynecol*. 2020;56(2):298-312.
9. Cohn HE, Sacks EJ, Heymann MA, Rudolph AM. Cardiovascular responses to hypoxemia and acidemia in fetal lambs. *Am J Obstet Gynecol*. 1974;120(6):817-824.
10. Sheldon RE, Peeters LL, Jones MD, Makowski EL, Meschia G. Redistribution of cardiac output and oxygen delivery in the hypoxemic fetal lamb. *Am J Obstet Gynecol*. 1979;135(8):1071-1078.
11. Yates DT, Green AS, Limesand SW. Catecholamines mediate multiple fetal adaptations during placental insufficiency that contribute to intrauterine growth restriction: lessons from hyperthermic sheep. *J Pregnancy*. 2011;2011:740408.
12. Bibeau K, Battista MC, Houde V, Brochu M. Fetal adrenal gland alterations in a rat model of adverse intrauterine environment. *Am J Physiol Regul Integr Comp Physiol*. 2010;298(4):R899-R911.
13. Lewis E, Kurtz AB, Dubbins PA, Wapner RJ, Goldberg BB. Real-time ultrasonographic evaluation of normal fetal adrenal glands. *J Ultrasound Med*. 1982;1(7):265-270.
14. van Vuuren SH, van der Doef R, Cohen-Overbeek TE, Goldschmeding R, Pistorius LR, de Jong TP. Compensatory enlargement of a solitary functioning kidney during fetal development. *Ultrasound Obstet Gynecol*. 2012;40(6):665-668.
15. Helfer TM, Rolo LC, Okasaki NA, et al. Reference ranges of fetal adrenal gland and fetal zone volumes between 24 and 37 + 6 weeks of gestation by three-dimensional ultrasound. *J Matern Fetal Neonatal Med*. 2017;30(5):568-573.
16. Turan OM, Turan S, Funai EF, Buhimschi IA, Copel JA, Buhimschi CS. Fetal adrenal gland volume: a novel method to identify women at risk for impending preterm birth. *Obstet Gynecol*. 2007;109(4):855-862.
17. Turan OM, Turan S, Funai EF, et al. Ultrasound measurement of fetal adrenal gland enlargement: an accurate predictor of preterm birth. *Am J Obstet Gynecol*. 2011;204(4):311.e1-311.e10.

18. Mari G, Uerpairojkit B, Abuhamad AZ, Copel JA. Adrenal artery velocity waveforms in the appropriate and small-for-gestational-age fetus. *Ultrasound Obstet Gynecol*. 1996;8(2):82-86.
19. Farzad Mohajeri Z, Aalipour S, Sheikh M, et al. Ultrasound measurement of fetal adrenal gland in fetuses with intrauterine growth restriction, an early predictive method for adverse outcomes. *J Matern Fetal Neonatal Med*. 2019;32(9):1485-1491.
20. Heese S, Hammer K, Möllers M, et al. Adrenal gland size in growth restricted fetuses. *J Perinat Med*. 2018;46(8):900-904.
21. Sennaiyan UN, Melov SJ, Arcus C, Kirby A, Alahakoon TI. Fetal adrenal gland: total gland volume and fetal zone to total gland ratio as markers of small for gestational age. *J Clin Ultrasound*. 2020;48(7):377-387.
22. Tekay A, Jouppila P. Fetal adrenal artery velocimetry measurements in appropriate-for-gestational age and intrauterine growth-restricted fetuses. *Ultrasound Obstet Gynecol*. 2000;16(5):419-424.
23. Blue NR, Hoffman M, Allshouse AA, et al. Antenatal fetal adrenal measurements at 22 to 30 weeks' gestation, fetal growth restriction, and perinatal morbidity. *Am J Perinatol*. 2021;38(7):676-682.
24. Paladini D, Rustico M, Viora E, et al. Fetal size charts for the Italian population. Normative curves of head, abdomen and long bones. *Prenat Diagn*. 2005;25(6):456-464.
25. Gómez O, Figueras F, Fernández S, et al. Reference ranges for uterine artery mean pulsatility index at 11-41 weeks of gestation. *Ultrasound Obstet Gynecol*. 2008;32(2):128-132.
26. Todros T, Ronco G, Fianchino O, et al. Accuracy of the umbilical arteries Doppler flow velocity waveforms in detecting adverse perinatal outcomes in a high-risk population. *Acta Obstet Gynecol Scand*. 1996;75(2):113-119.
27. Poudel R, McMillen IC, Dunn SL, Zhang S, Morrison JL. Impact of chronic hypoxemia on blood flow to the brain, heart, and adrenal gland in the late-gestation IUGR sheep fetus. *Am J Physiol Regul Integr Comp Physiol*. 2015;308(3):R151-R162.
28. Phillips ID, Simonetta G, Owens JA, Robinson JS, Clarke IJ, McMillen IC. Placental restriction alters the functional development of the pituitary-adrenal axis in the sheep fetus during late gestation. *Pediatr Res*. 1996;40(6):861-866.
29. Simonetta G, Rourke AK, Owens JA, Robinson JS, McMillen IC. Impact of placental restriction on the development of the sympathoadrenal system. *Pediatr Res*. 1997;42(6):805-811.
30. Samuelsson AM. New perspectives on the origin of hypertension; the role of the hypothalamic melanocortin system. *Exp Physiol*. 2014;99(9):1110-1115.
31. Taylor PD, Samuelsson AM, Poston L. Maternal obesity and the developmental programming of hypertension: a role for leptin. *Acta Physiol (Oxf)*. 2014;210(3):508-523.
32. Grandvuillemin I, Buffat C, Boubred F, et al. Arginase upregulation and eNOS uncoupling contribute to impaired endothelium-dependent vasodilation in a rat model of intrauterine growth restriction. *Am J Physiol Regul Integr Comp Physiol*. 2018;315(3):R509-R520.
33. Mizuno M, Siddique K, Baum M, Smith SA. Prenatal programming of hypertension induces sympathetic overactivity in response to physical stress. *Hypertension*. 2013;61(1):180-186.
34. Lurbe E, Garcia-Vicent C, Torro I, et al. First-year blood pressure increase steepest in low birthweight newborns. *J Hypertens*. 2007;25(1):81-86.
35. Yadav A, Beilin LJ, Huang RC, et al. The relationship between intrauterine foetal growth trajectories and blood pressure in young adults. *J Hypertens*. 2022;40(3):478-489.
36. Gamborg M, Byberg L, Rasmussen F, et al. Birth weight and systolic blood pressure in adolescence and adulthood: meta-regression analysis of sex- and age-specific results from 20 Nordic studies. *Am J Epidemiol*. 2007;166(6):634-645.
37. Huxley RR, Shiell AW, Law CM. The role of size at birth and postnatal catch-up growth in determining systolic blood pressure: a systematic review of the literature. *J Hypertens*. 2000;18(7):815-831.
38. Dodic M, May CN, Wintour EM, Coghlan JP. An early prenatal exposure to excess glucocorticoid leads to hypertensive offspring in sheep. *Clin Sci (Lond)*. 1998;94(2):149-155.

How to cite this article: Martinelli S, Rolfo A, Pace C, et al. Anatomical and functional changes of the fetal adrenal gland in intrauterine growth restriction. *Int J Gynecol Obstet*. 2024;00:1-8. doi:10.1002/ijgo.15491