Original Article

Fetotoxic risk of AT1 blockers exceeds that of angiotensin-converting enzyme inhibitors: an observational study

Corinna Weber-Schoendorfer[a], Angela Kayser[a], Tatjana Tissen-Diabaté[a], Ursula Winterfeld[b], Georgios Eleftheriou[c], Bernke Te Winkel[d], Orna Diav-Citrin[e,f], Amanda Greenall[g] Maria Hoeltzenbein[a,*], and Christof Schaefer[a,*]

Objective: The fetotoxic potential of prenatal exposure to angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin II receptor blockers (ARBs) has been known for many years. Symptoms range from transient oligohydramnios to neonatal anuria and permanent renal damage, joint contractures, hypocalvaria, lung hypoplasia and intrauterine or neonatal death. This study aims to investigate the critical gestational time for renin–angiotensin system inhibitor (RAS-I)-induced fetopathy, to quantify the fetopathy risk and to evaluate factors associated with the occurrence and severity of fetopathy.

Methods: Prospectively and retrospectively ascertained RAS-I exposed pregnancies from the databases of six teratology information services were analyzed.

Results: Eighty-nine pregnancies with ACE-I and 101 with ARB exposure beyond the first trimester were identified. Fifty-nine of these 190 pregnancies were classified as having evidence of RAS-I fetopathy. All pregnancies affected with fetopathy were exposed after 20 0/7 gestational weeks. Limited to prospectively enrolled cases with exposure at least 20 0/7 gestational weeks, the rate of fetopathy was 3.2% for ACE-I and 29.2% for ARB. The chance of recovery of amniotic fluid volume was higher with RAS-I discontinuation before 30 gestational weeks and with a longer exposure-free interval before delivery.

Conclusion: Exposure to ARBs is associated with a higher fetopathy risk than exposure to ACE-Is. RAS-I should ideally be discontinued prior to pregnancy or immediately after recognition of pregnancy. Because symptoms may improve in cases of RAS-I-induced oligohydramnios, pregnancy should be maintained as long as there is fetal well being. Physicians and patients need to be alerted to the fetotoxic risks of RAS-I.

Keywords: abnormalities, angiotensin II type 2 receptor blocker, angiotensin-converting enzyme inhibitor, fetopathy, fetus, humans, hypertension, oligohydramnios, pregnancy, venous thrombosis

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; aRR, adjusted relative risk; DDD, defined daily dosage; HCP, healthcare professional; IQR, interquartile range; RAS-I, renin–angiotensin system inhibitor; TIS, teratology information service; TOPFA, termination of pregnancy for fetal anomalies

INTRODUCTION

Renin–angiotensin system inhibitors (RAS-I), particularly angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin II receptor blockers (ARBs), are commonly used in the treatment of hypertension and are often prescribed for women of reproductive age. In Germany, 55% of antihypertensive prescriptions to the general population are RAS-I [1]. Due to their known fetotoxic effects, RAS-I are not recommended during the first trimester and are contraindicated during the second and third trimester of pregnancy.

Captopril was the first ACE-I introduced in 1981. Soon after, a report of a neonate with persistent anuria after prenatal exposure was published [2]. In 1989, Rosa evaluated seven published case reports with adverse fetal outcome and pointed to the relationship between late pregnancy exposure and adverse fetal effects such as oligohydramnios, and related sequelae, including anuria, hypoplastic kidneys and lungs, hypocalvaria, joint

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[a]Charité – Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Pharmakovigilanzzentrum Embryonaltoxikologie, Institut für Klinische Pharmakologie und Toxikologie, Berlin, Germany, [b]Swiss Teratogen Information Service and Service of Clinical Pharmacology, University Hospital of Lausanne, Lausanne, Switzerland, [c]Poison Control Center, Bergamo, Italy, [d]Teratology Information Service, Netherlands Pharmacovigilance Centre Lareb, 's-Hertogenbosch, The Netherlands, [e]The Israeli Teratology Information Service, Israel Ministry of Health, [f]The Hebrew University Hadassah Medical School, Jerusalem, Israel and [g]The UK Teratology Information Service, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, UK

Correspondence to Corinna Weber-Schoendorfer, Charité Universitätsmedizin Berlin, Pharmakovigilanzzentrum Embryonaltoxikologie, Augustenburger Platz 1, D-13353 Berlin, Germany. Tel: +00 49 30 450525711; fax: +00 49 30 4507525920; e-mail: corinna.weber-schoendorfer@charite.de

*Maria Hoeltzenbein and Christof Schaefer contributed equally to the article.

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contractures and hypotension [3]. An ACE-I fetopathy was proposed in 1993 [4]. Numerous further case reports and case series have since been published, for example [5].

Losartan was the first approved ARB in Europe in 1994. Unsurprisingly, given that both ACE-Is and ARBs exert their effect by suppressing the renin–angiotensin system, similar adverse fetal and neonatal outcome following gestational ARB exposure were soon reported [6]. Despite warnings on RAS-I use in pregnancy in product information and medical journals, for example [7,8], RAS-I treatment during the second and third trimesters of pregnancy still occurs.

Decreased fetal renal vascular tone is thought to trigger the fetopathy, and leads to reduced urine production, oligohydramnios and related symptoms [9]. The reported effects of RAS-I fetotoxicity range from oligohydramnios [10], to postnatal acute renal failure [11], long-term renal damage even after transient recovery after birth [12], and intrauterine [13] or postnatal death [14]. There are also reports of unremarkable pregnancy outcomes [15].

The primary objectives of this observational study were to define the onset of the critical gestational time window for fetotoxic risk, to quantify the risk of a RAS-I fetopathy after ACE-I and ARB exposure and to evaluate risk factors associated with the occurrence of fetopathy.

METHODS

Participating sites

Six teratology information services (TISs) participated in the study: Berlin (Germany), Lausanne (Switzerland), Bergamo (Italy), Jerusalem (Israel), Newcastle (the United Kingdom) and s-Hertogenbosch (the Netherlands). TISs offer risk assessment on drug use during pregnancy to healthcare professionals (HCPs) and pregnant women either seeking advice regarding the risk of a medication during an ongoing unremarkable pregnancy or a suspected causal relationship in case of adverse effects after prenatal drug exposure.

Most consultations take place during early pregnancy before pregnancy outcome or results of prenatal diagnostic tests are known. Follow-up of these pregnancies is considered prospective. In addition, TISs run retrospective case registries with suspected adverse reactions of drug use during pregnancy reported from HCPs, medical authorities and pregnant women. A distinct phenotype observed in a few fetuses/infants may support a signal of fetotoxicity. In addition, exposure characteristics are helpful to specify preconditions of fetotoxic effects.

Data acquisition

RAS-I exposed pregnancies were retrieved from the database of the participating TISs. Included were all completed follow-up cases with second and/or third trimester RAS-I exposure and first TIS contact until 31 December 2016 for prospective and until 31 January 2018 for retrospective cases. For methods of case identification in TIS Berlin, see Supplemental Figs. S1 and S2, http://links.lww.com/HJH/B144.

TISs use standardized questionnaires at first contact and for follow-up on course and outcome of pregnancy. All relevant data in respect to drug exposure, maternal characteristics, obstetric and family history as well as prenatal diagnostics, course and complications of pregnancy and delivery and pregnancy outcome are documented. Information on gestational age at delivery, infant's sex, birth weight, length, head circumference, Apgar scores and any anomalies are requested [16]. Whenever necessary, medical records are asked for. For this study, information on amniotic fluid, prenatal and postnatal kidney ultrasound and kidney function were retrieved.

Definitions

We considered the presence of one or more of the following symptoms as indicative of RAS-I fetopathy: oligohydramnios/anhydramnios, neonatal renal impairment with or without oligouria/anuria, joint contractures, hypocalvaria/widened skull sutures and pulmonary hypoplasia [17]. Thrombosis of vena cava was regarded as part of the RAS-I fetopathy, if associated with at least one of the other characteristic signs [18].

Gestational age was estimated by ultrasound during the first trimester or, if not available, calculated from the first day of the last menstrual period. Stillbirth was defined as loss of a fetus more than 500 g (or if weight was not available $\geq$24 gestational weeks after the last menstrual period) and neonatal death as death of a live born infant within 28 days. Small for gestational age was defined as an infant with a birth weight less than 10th percentile for sex and gestational age at delivery. Reference for birth weight percentiles was the German perinatal survey from 2007 to 2011 [19]. Preterm birth was defined as delivery at less than 37 completed weeks' gestation. The beginning of the second trimester was set at gestational week 13 0/7.

Analyses

We evaluated our data as followed: independent of prospective or retrospective ascertainment, first, all cases were assessed for fulfilling the established criteria for RAS-I fetopathy and screened for related symptoms not yet recognized as RAS-I features; second, all cases assigned to RAS-I fetopathy were evaluated for RAS-I exposure interval to identify the beginning of the vulnerable time window; third, subsequently, all fetopathy cases (prospective and retrospective) were compared with nonfetopathy cases exposed during the sensitive high-risk exposure interval to screen for maternal or treatment characteristics that could have contributed to the occurrence of fetopathy; fourth, limited to prospectively ascertained cases exposed in the preassigned vulnerable interval, the relative risk (RR) for fetopathy was calculated for ACE-Is and ARBs (Table 1 and Fig. S3, http://links.lww.com/HJH/B144).

RAS-I fetopathy was measured by a binary variable indicating whether the infant displayed fetopathy signs. Cases were independently classified as RAS-I fetopathy by four of the authors (A.K., C.S., C.W.S., M.H.). Authors were blinded to retrospective/prospective case ascertainment and timing of RAS-I exposure.

For the statistical analyses, descriptive and exploratory methods were applied. Maternal and neonatal characteristics as well as drug specifications were analyzed to identify possible factors associated with RAS-I fetopathy and confounding. Continuous variables were summarized with median, interquartile range and the minimum and maximum values. For categorical variables counts and relative

TABLE 1. Overview on numbers of exposed pregnancies (2nd and 3rd trimester) and fetopathy

	N	Fetopathy	
		Yes, *n* (%)	*n*
Prospective cases	121	8 (6.6)	113
ACE-I exposed	70	1 (1.4)	69
ARB exposed	51	7 (13.7)	44
Prospective cases, exposed during high-risk period (GW ≥ 20 0/7)	55	8 (14.5)	47
ACE-I exposed	31	**1 (3.2)**[a]	30
ARB exposed	24	**7 (29.2)**[b]	17
Retrospective cases	69	51 (73.9)	18
(GW ≥ 20 0/7)	68	51 (75.0)	17
ACE-I exposed	18	5 (26.3)	13
ARB exposed	50	46 (92.0)	4

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; GW, gestational week.
[a]This value corresponds to the fetopathy rate of ACE-I exposed pregnancies.
[b]This value corresponds to the fetopathy rate of ARB exposed pregnancies.

frequencies were used. Graphical methods displaying pregnancy course and exposure time were applied to explore associations between drug exposure and fetopathy signs. Early vs. late RAS-I discontinuation and recovery of oligohydramnios were analyzed using *t* test. We performed Poisson regression analyses to explore associations between the number of fetopathy signs per case and ARB/ACE-I exposure. Adjusted RRs (aRRs) were estimated taking into account data heterogeneity by including the covariates retrospective ascertainment, preterm birth, maternal age, recovery time and cotherapy with diuretics. To compare dosages of the different substances by fetopathy status, mean dosages per substance were contrasted with the respective defined daily dosages (DDDs) [20]. A value of 1 means that the mean dose of our sample corresponds to the DDD.

Statistical analyses were performed using R version 3.5.1 (R Development Core Team, Vienna, Austria, 2017).

Informed consent and approval

Data are presented in accordance with the recommendations of the Strengthening the Reporting of Observational Studies in Epidemiology statement [21] and are in line with the declaration of Helsinki [22]. This is a noninterventional observational study using archived data. All patients were informed about data privacy, data collection and usage of their data and agreed on it. An identification of individual patients by means of this study is not possible.

The study protocol was approved by the ethics committee at the Charité-Universitätsmedizin Berlin (EA2/116/16) and the study was registered at DRKS00011568.

RESULTS

In total, 190 pregnancies exposed to RAS-I during the second and/or third trimester were included in this study: 173 were identified by TIS Berlin (of which 44 ARB-exposed pregnancies had been previously published [18]), eight by TIS Lausanne, and collectively, nine by TIS Bergamo, Jerusalem, Newcastle and s-Hertogenbosch. Eighty-nine of the 190 pregnancies were exposed to ACE-I and 101 to ARB (Table 1 and Fig. S3, http://links.lww.com/HJH/B144).

TABLE 2. Comparison of maternal characteristics of pregnancies exposed during the high-risk period (≥20 0/7 gestational weeks), *n* = 123

	Fetopathy	Nonfetopathy
N	59	64
ARB, *n*	53	21
ACE-I, *n*	6	43
Combination with diuretics, *n* (%)	24 (40.7)	20 (31.3)
Concomitant RAS-I	1× ramipril, 1× aliskiren	1× ramipril
RAS-I < GW 30 0/7	31 (all ARB)	38 (24 ACE-I + 14 ARB)
RAS-I ≥ GW 30 0/7	28 (6 ACE-I + 49 ARB)	26 (20 ACE-I + 6 ARB)
Drug treatment indication, *n*	58	64
Chronic art. hypertension, *n* (%)	53 (91.4)	57 (89)
Renal hypertension, *n*	1	0
Cardiomyopathy, *n*	3	2
Gestational hypertension, *n*	0	1
Others, *n*	1	4
Maternal age, *n*	54	61
Age (years)	36 (31–38) (25–44)	33 (29–38) (21–48)
BMI, *n*	37	43
BMI (kg/m^2)	32.1 (24.8–38.7) (19–51.3)	30.5 (26.3–40.2) (18.3–61.6)
Smoking, *n*	41	57
No (%)	34 (82.9)	42 (73.7)
≤5 cig/day, *n* (%)	1 (2.4)	3 (5.3)
>5 cig/day, *n* (%)	6 (14.6)	12 (21.1)
Alcohol, *n*	41	54
No, *n* (%)	37 (90.2)	51 (94.4)
≤1 drink/day, *n* (%)	3 (7.3)	3 (5.6)
>1 drink/day, *n* (%)	1 (2.4)	0 (0)
Social drugs, *n*	37	53
No, *n* (%)	37 (100)	52 (98.1)
Yes, *n* (%)	0 (0)	1 (1.9)
Previous pregnancies, *n*	54	62
0, *n* (%)	20 (37.0)	22 (35.5)
1, *n* (%)	15 (27.8)	11 (17.7)
2, *n* (%)	8 (14.8)	11 (17.7)
3 or more, *n* (%)	11 (20.4)	18 (29.0)
Previous parities, *n*	56	62
0, *n* (%)	26 (46.4)	25 (40.3)
1, *n* (%)	14 (25.0)	14 (22.6)
2, *n* (%)	10 (17.9)	13 (21.0)
3 or more, *n* (%)	6 (10.7)	10 (16.1)
Diabetes, *n*	38/59	41/64
No, *n*	24	22
Yes, *n* (%)	14[a] (37)	19 (46)
Type 1, *n*	0	2
Type 2, *n*	3	10
Gestational diabetes, *n*	10	7

For maternal age, BMI and gestational week at first contact, median, interquartile range (IQR), and min/max are presented. ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; RAS-I, renin–angiotensin system inhibitor; GW, gestational week; IQR, interquartile range; RAS-I, renin–angiotensin system inhibitor.
[a]One case with unknown type of diabetes.

Altogether 59 cases were classified as having evidence for RAS-I fetopathy. As all infants/fetuses with fetopathy were exposed at least until gestational week 20 0/7, treatment after gestational week 20 was considered as the high-risk period and thus this subgroup was further analyzed.

Risk factors associated with the occurrence of fetopathy

To investigate whether there were factors associated with the occurrence of fetopathy, we compared maternal and treatment characteristics between 'fetopathy' and 'nonfetopathy' cases with exposure at least 20 0/7 gestational weeks (Table 2). Apart from the striking dominance of ARBs in the

fetopathy group (Fig. S3, http://links.lww.com/HJH/B144), 'fetopathy mothers' were older (36 vs. 33 years), had a higher BMI (32.1 vs. 30.5 kg/m^2) and were more often concomitantly treated during the second and/or third trimester with diuretics (40.7 vs. 31.3%). These differences were NS (data not shown). A comparison of individual daily dosages of the high-risk period cases by fetopathy status with the respective DDDs resulted in a mean value of 1.4 for both, fetopathy and nonfetopathy cases. (Two spikes of nonfetopathy cases with ramipril exposure were excluded from analyses, because dosages seem doubtfully high.) The rates of specific indications for drug treatment did not differ significantly between fetopathy cases and nonfetopathy cases.

Exposure pattern, pregnancy course and outcome

Figure 1 shows exposure pattern, pregnancy course and pregnancy outcome of cases with fetopathy. The shortest duration of exposure in a fetopathy pregnancy was 15 days (Fig. 1, no 124: losartan gestational week 28–30). For exposure patterns and pregnancy outcomes of pregnancies without fetopathy see Fig. S4, http://links.lww.com/HJH/B144.

In pregnancies with RAS-I exposure at least 20 0/7 gestational weeks, the drug was discontinued at a median gestational week of 28 3/7 in fetopathy cases and at 27 6/7 in nonfetopathy cases. However, the median time from drug cessation until delivery was 2 1/7 weeks for fetopathy cases [interquartile range (IQR) 0.0–11.18; min 0, max 18] and 8 5/7 weeks for nonfetopathy cases (IQR 0.72–15.36; min 0, max 21).

For pregnancy outcomes of fetopathy and nonfetopathy cases with exposure during the high-risk period see Table 3. Infant death, neonatal death and termination of pregnancy for fetal anomalies (TOPFA) occurred more often in the fetopathy group. The majority of infants with fetopathy were born preterm (71 vs. 29% in the nonfetopathy group). Sex and gestational week-adapted SD scores for birth weights were on average negative for both, the fetopathy and nonfetopathy group, but were not significantly different from the zero, that is from average population values (Table 3).

Oligohydramnios: first clinical symptom of fetopathy

Fifty-three of the 59 fetopathy cases had a confirmed oligo/anhydramnios. In two of the remaining cases, pregnancy was not recognized prior to delivery (Fig. 1, no. 5: ramipril and no. 60: enalapril). In addition, there were conflicting data in two (Fig. 1, no. 40: olmesartan and no. 165: olmesartan) and no oligohydramnios in two further cases (Fig. 1, no. 172: enalapril and no. 49: olmesartan).

In 15 of the 59 fetopathy cases oligo/anhydramnios was the only symptom of RAS-I fetopathy. These included one ACE-I case with drug exposure until delivery at week 35 5/7 (Fig. 1 and S3, no. 181) and 14 ARB-exposed cases with discontinuation at a median gestational week of 23 1/7 (min 20 0/7; max 26 2/7). Normalization of amniotic fluid volume following drug discontinuation occurred in 12 of the 15 pregnancies within 2–5 2/7 weeks. In the three remaining pregnancies, the medication was either not discontinued (the ACE-I case) or the pregnancy was not ongoing (one TOPFA and one stillbirth, see Figs. 1 and 2, no. 152 and no. 117).

Figure 2 shows the relationship between time of diagnosis of oligohydramnios ($n = 53$), cessation of RAS-I therapy, gestational week at delivery, pregnancy outcome and whether or not amniotic fluid volume normalized. Earlier drug discontinuation was significantly associated with recovery of oligohydramnios ($P < 0.01$). Of note, in 10 pregnancies RAS-I therapy was not stopped within 3 days of the diagnosis of oligohydramnios.

Infants' fetopathy symptoms

Altogether, 38 infants presented with some kind of postnatal renal involvement (Fig. 1 and Table S2, http://links.lww.com/HJH/B144): 29 neonates had a diagnosis of renal insufficiency and 17 experienced transient or permanent oliguria/anuria with peritoneal dialysis required in 10 cases. Nine out of 10 dialysed infants had been exposed until delivery (Fig. 1, no. 5: ramipril, no. 21: valsartan, no. 24: valsartan, no. 49: olmesartan, no. 89: valsartan, no. 105: ramipril, no. 140: valsartan, no. 151: valsartan, no. 164: candesartan, and no. 174: candesartan). In 30 of the 38 infants, abnormal postnatal kidney ultrasound was documented. The majority of these presented with hyperechogenic and enlarged kidneys often with poor differentiation of the proximal tubules. A minority additionally showed multiple small cysts. Tubular dysplasia/dysgenesis was documented in nine infants.

Pulmonary hypoplasia was confirmed in 11 of the 59 fetopathy cases: eight infants died shortly after birth; one of the remaining pregnancies was terminated due to poor prognosis (Fig. 1, no. 170) and two infants survived (Fig. 1, no. 133: candesartan and no. 185: candesartan). RAS-I therapy was continued in seven of 11 until or almost until delivery. All affected children were ARB exposed.

Five infants presented with vena cava and/or renal thrombosis. Oppermann *et al.* [18] previously described three of these cases.

Thalamostriatal vasculopathy was observed in two infants by cranial ultrasound (Fig. 1, no. 86: candesartan and no. 95: olmesartan). One of these cases has already been published by Wegleiter *et al.* [23].

Finally, we investigated the association between the number of fetopathy signs per case and exposure group (Fig. 1 and Table S2, http://links.lww.com/HJH/B144). The number of fetopathy signs was strongly related to the ARB exposure group (aRR 6.04; 95% confidence interval 2.29–15.92).

Fetopathy rate in prospectively ascertained pregnancies

Fifty-five prospective cases were exposed during the high-risk period with a rate of fetopathy for ARB exposed infants/fetuses of 29.2% (7/24) and for ACE-I of 3.2% (1/31) (Table 1 and Fig. S3, http://links.lww.com/HJH/B144).

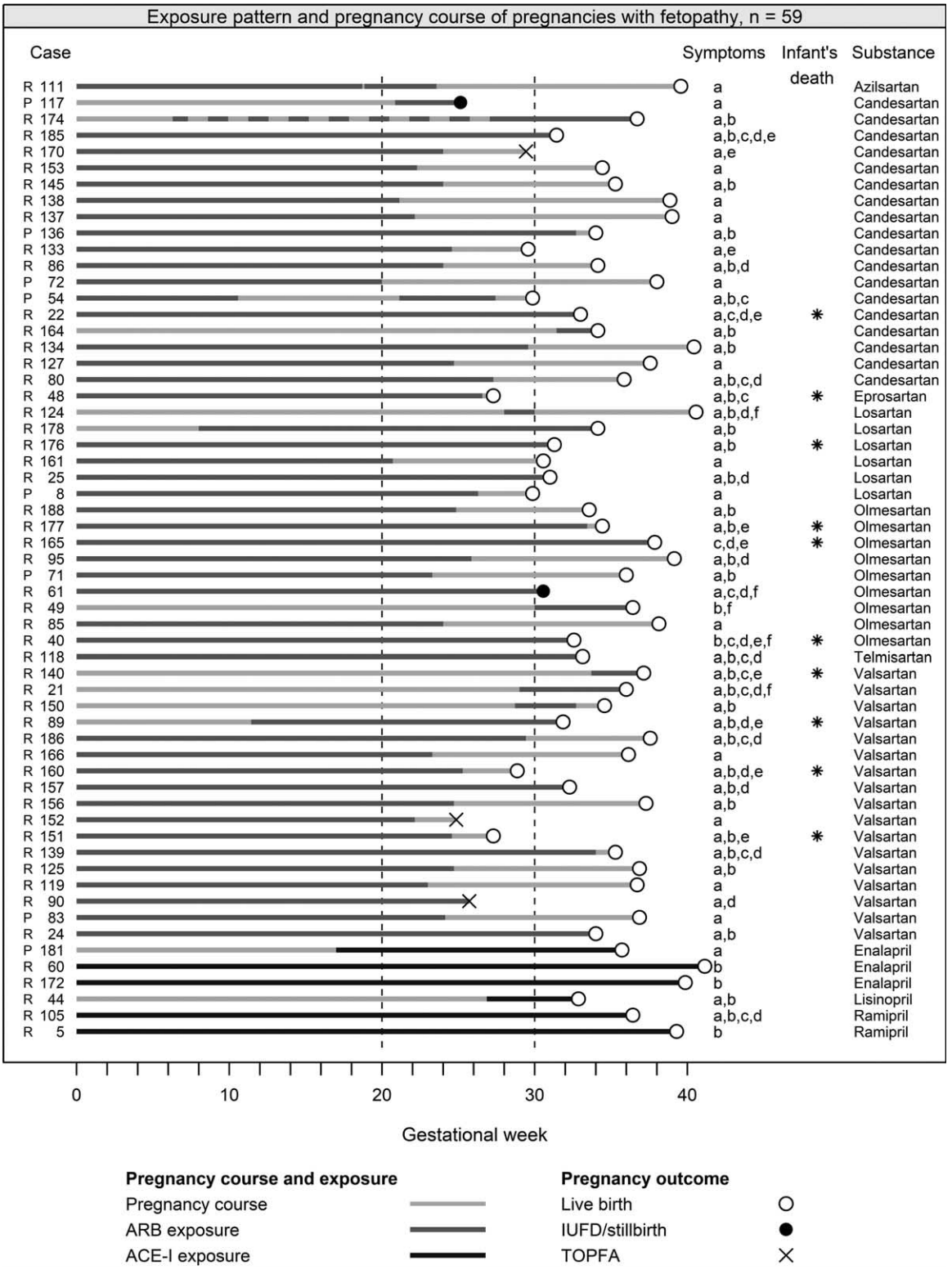

FIGURE 1 Outcomes of renin–angiotensin system inhibitor exposed pregnancies with fetopathy. Each line symbolizes one pregnancy. (a) Oligo/anhydramnios; (b) postnatal renal involvement; (c) contractures; (d) widened sutures; (e) lung hypoplasia; (f) infant's thrombosis (vena cava/renal thrombosis). IUFD, intrauterine fetal death; P, prospectively ascertained cases; R, retrospectively ascertained cases; TOPFA, termination of pregnancy for fetal anomalies. *Infant's death.

DISCUSSION

We analyzed pregnancy outcomes of 190 cases with RAS-I exposure after the 1st trimester to define the onset of the high-risk period for fetotoxic effects. We further intended to quantify the risk of fetopathy after ARB and ACE-I exposure, and to evaluate risk factors associated with the occurrence of fetopathy.

TABLE 3. Pregnancy outcomes in cases exposed during the high-risk period (≥20.0/7 gestational weeks) by presence of fetopathy (*n* = 123)

	Fetopathy	Nonfetopathy
Pregnancy outcomes, *N*	59	64
Live-born infants, *n*	54	62
Stillbirth (≥500 g), *n*	2	2
TOPFA, *n*	3	0
GW at delivery, *N*	54	62
GW at delivery, in weeks, median (IQR)	35.5 (32.9–37.5)	38.36 (36.25–39.97)
(min/max)	(27.29–41.14)	(24.57–41.14)
Preterm infants, *n* (% live-borns)	38 (72%)	18 (29%)
Birth weight, *N*	51	62
Birth weight, in g, median	2365	3015
(IQR) (min/max)	(1661–2945) (720–3940)	(2665–3541) (580–4700)
Small-for-age infants, *n*/*N* (%)	9/51 (17.6)	12/62 (19.4)
Median SDS for birth weight	−0.39	−0.26
(IQR)	(−1.10–0.19)	(−0.92–0.77)
(Min/max)	(−2.13–1.34)	(−2.68–2.62)
Breech presentation, *n*	15[a]	5
C-section, *n* (%)	37 (68.5)	38 (61.3)
Infant death within 1 year of age, *n*	10[b]	1[c]

GW, gestational week; IQR, interquartile range; SDS, SD scores; TOPFA, termination of pregnancy for fetal anomalies.
[a]Including one transverse presentation and one unspecified malposition.
[b]Seven neonatal deaths and three deaths occurring at 20, 25 and 35 weeks of age.
[c]Died aged 20 weeks because of prematurity-related problems. GW at birth 24 4/7, 580 g.

High-risk gestational period and quantification of fetopathy risks by renin–angiotensin system inhibitor group

In our study, RAS-I fetopathy symptoms were exclusively observed when exposure lasted at least until gestational week 20 0/7. This is in accordance with the findings of other authors, for example [24,25].

Fetopathy-related symptoms were much more prevalent among ARB exposed (29%) compared with ACE-I (3%). This notable risk difference between the two groups is in line with the study of Bullo *et al.* [15], who reviewed 118 published cases with prenatal ACE-I exposure and 68 with prenatal ARB exposure. The authors found an overall rate of 48% for any complication for ACE-I exposed and 87% for ARB-exposed neonates. However, the study probably overestimated the risk, because of publication bias and inclusion of various noncharacteristic fetopathy signs, such as arterial hypotension, respiratory distress syndrome, persistent patent ductus arteriosus, limb defects, intrauterine growth retardation, cerebral complications and fetal or neonatal death including miscarriages.

Therefore, our analysis focusing on fetopathy-specific features in prospectively-reported pregnancies provide more reliable estimates of fetopathy rates.

Risk factors associated with the occurrence of fetopathy

In fetopathy cases, we ascertained a nonsignificantly higher maternal age and BMI as well as a more frequent comedication with diuretics. Surprisingly, RAS-I dose was not different between fetopathy and nonfetopathy cases and median gestational week at discontinuation differed only by 4 days. Our study does not seem to support the assumption that the above factors are responsible for the development of fetopathy. However, the limited sample size of the study should be taken into consideration.

The median exposure-free time interval until delivery differed by 6 weeks and 4 days between fetopathy and nonfetopathy cases. This can partially be explained by an earlier median gestational age at delivery in the fetopathy group (gestational week 35.5 vs. 38.4). However, fetopathy itself might have led to an earlier gestational age at delivery. On the other hand, prematurity is a major risk factor for adverse infant's outcome. Due to this mutual influence, the interpretation of the longer RAS-I-free interval in the nonfetopathy group should be made cautiously.

Amniotic fluid volume and severity of fetopathy

Normalization of amniotic fluid volume was associated with the greater RAS-I-free interval before delivery and RAS-I discontinuation before gestational week 30 (Fig. 2). Shimada *et al.* [24] performed a literature review of 83 ARB exposed cases and came to a similar conclusion.

In pregnancies with oligohydramnios as the only visible (and reversible) symptom, recovery of amniotic fluid took 2–5 2/7 weeks. Spaggiari *et al.* [25] reported similar findings.

In contrast, in the most severely affected infants in our study, who needed peritoneal dialysis and/or exhibited pulmonary hypoplasia, there was no or little time between discontinuation of RAS-I and delivery (Fig. 1).

Persistent oligohydramnios may indicate persistent renal impairment with the risk of postnatal anuria. In addition, joint contractures, hypoplastic skull bones/widened skull sutures and lung hypoplasia may result from ongoing renal impairment caused by continuous RAS-I medication. Recovery of amniotic fluid volume may lead to improvement of associated effects on other organs. This was

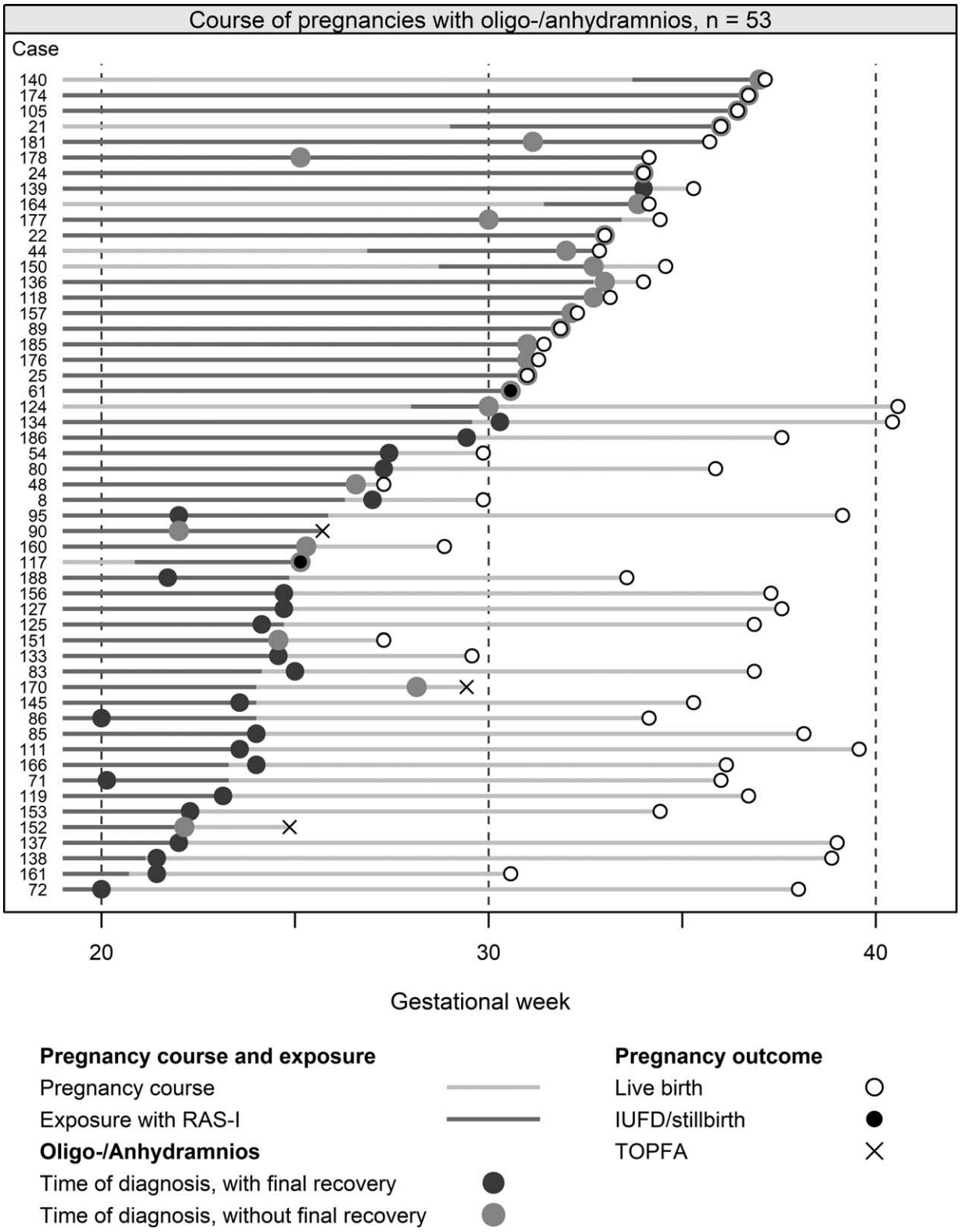

FIGURE 2 Relationship between gestational week at diagnosis of oligohydramnios, recovery of amniotic fluid volume, treatment duration, gestational week at delivery and pregnancy outcome. IUFD, intrauterine fetal death; TOPFA, termination of pregnancy for fetal anomalies.

observed in one of our retrospective cases where candesartan exposure took place until gestational week 24 4/7, when oligohydramnios and thoracic hypoplasia were diagnosed. At gestational week 28 2/7 amniotic fluid had recovered and thorax development normalized. Due to deterioration of maternal cardiomyopathy, the infant was delivered prematurely at gestational week 29 4/7 with slightly hypoplastic lungs, but survived (Fig. 1, no 133).

Specific outcomes

RAS-I fetopathy without oligo/anhydramnios is a rare condition. Hinsberger *et al.* [26] and Nayar *et al.* [27] reported one pregnancy each with normal amniotic fluid during pregnancy, but transient anuria after birth. In our study, there were two pregnancies with normal amniotic fluid index despite neonatal renal anomalies (Fig. 1, no. 49: olmesartan and no. 172: enalapril).

Five infants presented with a vena cava thrombosis. Plazanet *et al.* [28] diagnosed a high thrombosis rate in autopsy of 14 RAS-I-exposed infants, which contrasted the low prevalence in our study and in other publications to date. This might point to underdiagnosis in milder cases or bias due to more detailed examinations in severely affected cases – especially after fetal/infant death.

Two infants exposed to RAS-I *in utero* presented with thalamostriatal vasculopathy [23]. This finding is otherwise noted in congenital cytomegalovirus infection. In both neonates, toxoplasmosis, other agents, rubella, cytomegalovirus and herpes simplex virus serology (TORCH serology) for intrauterine infections were negative. No further cases could be identified in the literature. This could be a chance finding or a not yet recognized feature of the fetopathy.

Why are renin–angiotensin system inhibitors prescribed in pregnancy despite contraindications?

Our data suggest that some cases of RAS-I exposure in later pregnancy are due to delayed recognition of pregnancy, particularly in obese women and in those with irregular menses. Furthermore, some HCPs disregard package leaflet warnings or even misinterpret the diagnosis of oligohydramnios. In 26 of our cases, therapy was initiated after conception (Fig. 1), and in 15 of these cases began after gestational week 12 6/7. There were 10 pregnancies, in which RAS-I therapy was not discontinued within 3 days after the diagnosis of oligohydramnios. Of note, five women had a previous pregnancy with exposure to an ARB. In addition, there were five women with continued RAS-I treatment who were pregnant via assisted reproduction. This underlines the importance of obtaining a careful medication history. Only in one patient was RAS-I therapy purposely continued during pregnancy because of severe maternal cardiomyopathy (Fig. 1, no. 133: candesartan. Case description see above.). In view of our study results, an ACE-I should be preferred, if treatment with a RAS-I during pregnancy is unavoidable.

Strengths and limitations

A limitation of this study is that detection and reporting of fetopathy features depend on the alertness and scrutiny of the engaged physicians. Therefore, our findings might underestimate the fetopathy risks and conditional characteristics. Oligohydramnios for example might have been missed in some of our cases, because of difficulties of defining oligohydramnios across gestational stages [29], and the late diagnosis of pregnancy.

Retrospective cases differed from prospective cases by an overestimation of adverse outcomes. Hence, more severely affected pregnancies, fetuses/neonates were among this group and drug treatment was discontinued later. However, fetopathy rate was calculated with prospectively ascertained pregnancies only. A reporting bias regarding the onset of the high-risk period and maternal characteristics seems unlikely.

Our study presents the largest number of ARB and ACE-I exposed pregnancies during the second and third trimester published so far. High-quality data recruitment across sites follows well established procedures [16].

In conclusion, in case of inadvertent use during pregnancy, RAS-I should be discontinued as soon as pregnancy is identified. In our study, fetopathy was not observed, if RAS-I exposure was ceased before gestational week 20. Fetotoxic risk of ARBs (29%) exceeds that of ACE-Is (3%) after exposure beyond gestational week 20. In cases of unavoidable RAS-I treatment during pregnancy ACE-I should be preferred over ARBs. Early detection of oligohydramnios followed by immediate discontinuation of RAS-I may lead to recovery from fetotoxic effects of RAS-I exposure. Induction of delivery should be avoided after RAS-I discontinuation as long as there is fetal well being to allow improvement of RAS-I-induced prenatal anomalies. Further studies are needed to analyze the long-term course of intrauterine RAS-I exposed infants. Patients, pharmacists and HCPs should be better trained regarding the fetotoxic risks of RAS-I.

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Conflicts of interest

There are no conflicts of interest.

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