RESEARCH ARTICLE

Acardiac twin pregnancies part V: Why does an acardiac twin with renal tissue produce polyhydramnios?

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Abstract

Background: Acardiac twinning is a complication of monochorionic twin pregnancies. From literature reports, 30 of 41 relatively large acardiac twins with renal tissue produced polyhydramnios within their amniotic compartment. We aim to investigate the underlying mechanisms that cause excess amniotic fluid using an established model of fetal fluid dynamics.

Methods: We assumed that acardiac onset is before 13 weeks, acardiacs with renal tissue have normal kidney function and produce urine flow from 11 weeks on, and acardiac urine production requires a pressure of half the pump twin's mean arterial pressure. We apply a resistance network with the pump twin's arterio-venous pressure as source, pump umbilical arteries, placenta, placental arterio-arterial (AA) anastomoses and acardiac resistances. Acardiac amniotic fluid dynamics excluded acardiac lung fluid secretion, swallowing and the relatively small intramembranous flow.

Results: In small acardiacs with sufficient urine production, polyhydramnios will occur due to the lack of amniotic fluid resorption. Urine production is dependent upon having sufficient mean arterial pressure, which requires nearly a two-fold larger resistance within the acardiac as compared to the placental AA resistance. Subphysiologic arterial pressure may result in renal dysgenesis.

Conclusion: Our findings suggest the potential for prediction of which clinical acardiac cases may or may not develop polyhydramnios based upon noninvasive assessments of renal tissue, blood flow and urine production. This information would be of great value in determining early obstetric interventions as opposed to conservative management. These findings may also contribute to an improved knowledge of the fascinating pathophysiology that surrounds acardiac twinning.

1 | INTRODUCTION

Acardiac twinning in monochorionic twin pregnancies requires a set of arterio-arterial (AA) and veno-venous (VV) placental anastomoses and cessation of cardiac function in the future acardiac twin. The incidence of this complication is 1:9500 to 12,000 pregnancies (van Gemert, van den Wijngaard, & Vandenbussche, 2015). The other twin, the pump twin, then perfuses the acardiac body through its aorta with deoxygenated arterial blood in a reversed direction compared to normal, hence the name Twin Reversed Arterial Perfusion (TRAP) sequence (Van Allen, Smith, & Shepard, 1983). Perfusion of the acardiac body by deoxygenated arterial blood causes the acardiac to grow but often as a bizarre malformed fetus. Without intervention, pump twin mortality is reported to be about 50% (Healey, 1994; Moore, Gale, & Benirschke, 1990; Van Allen et al., 1983).

In the last two decades, acardiac twins are predominantly diagnosed in the first trimester because of the scans performed nowadays to screen for congenital malformations and chromosomal abnormalities (e.g., Lewi, Valencia, Gonzalez, Deprest, & Nicolaides, 2010). Interestingly, acardiac formation beyond 13 weeks has never been observed. The reason for this is currently unknown.

In Healey's seminal paper on 184 acardiac twin cases, which aimed to identify factors that could predict survival rates of pump twins (Healey, 1994), it was reported that polyhydramnios occurred in 30 of the 41 acardiacs with proven renal tissue versus none of the 16 that lacked renal tissue. There was a significant association between the acardiac/pump birth weight ratio and polyhydramnios ($p = .036$). Unfortunately, neither gestational ages nor criteria used for diagnosing acardiac sac polyhydramnios were provided. As the development of excess amniotic fluid puts the pregnancy and viable twin at risk of prematurity, it is essential to understand the mechanism and develop therapeutic approaches to polyhydramnios. Healey (1994) reported that therapeutic amniocentesis was used in seven cases to relieve maternal discomfort, with a successful outcome in four and placental abruption, fetal death and preterm labor in the other three.

We sought to investigate the possible mechanisms that can cause polyhydramnios in acardiac twin amniotic sacs. This requires combining (A) a vascular resistance model of an acardiac monochorionic twin pregnancy with (B) modeling descriptions of (a) acardiac amniotic fluid dynamics, (b) acardiac urine production dynamics, (c) pump and acardiac development including acardiac blood pressures as produced by the pump twin, and (d) calculating blood pressures and flows within the resistance model. We will also apply our model to seven of our 18 (39%) acardiac cases (PGJN) where the acardiac twin had one or two kidneys.

2 | MATERIALS AND METHODS

2.1 | Vascular resistance scheme

Figure 1 shows the vascular resistance network used in this paper. It includes the pump twin's mean arterial and venous pressures (P_a^{Pu}, P_v^{Pu}), acting as pressure source here, the pump's umbilical arterial and placental resistances, the AA anastomotic resistance and the acardiac vascular resistance. We assumed that the pump twin remained unaffected by the acardiac twin, for example, blood pressures, oxygen saturation distribution, growth, organ perfusion, et cetera. The placenta of the twin that became the acardiac is now perfused by the pump twin (van Gemert, Ross, Nikkels, & van den Wijngaard, 2016). We neglected the VV and pump's umbilical venous resistances because they are significantly smaller than their
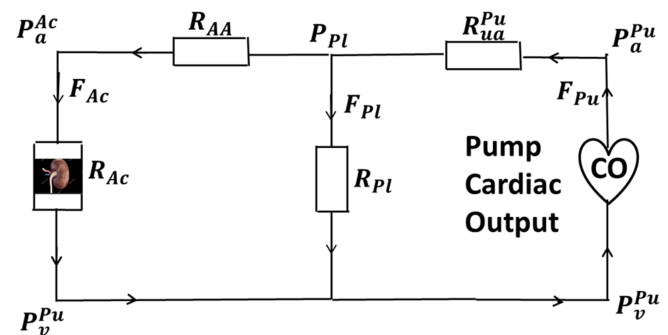

FIGURE 1 Resistance scheme of the acardiac monochorionic twin pregnancy. *CO*: Pump twin's cardiac output; *P*: pressures: subscripts *a,v*: arterial, venous, superscripts *Pu, Ac*: pump, acardiac; *F*: blood flows, subscripts *Pu, Ac, Pl*: pump, acardiac, placenta; *R*: vascular resistances, subscripts *ua, AA, Ac*: umbilical arteries, arterioarterial, acardiac

arterial counterparts (much larger diameters). As previously (van Gemert, van den Wijngaard, Paarlberg, Gardiner, & Nikkels, 2017), we included a 30% pressure loss of the pump's mean arterial pressure over the pump's umbilical arteries, based on fetal lamb data (Adamson, Whitely, & Langille, 1992), implying that the pressure source over the pump's placenta is given by $\left(0.7 \cdot P_a^{Pu} - P_v^{Pu}\right)$.

2.2 | Acardiac sac amniotic fluid dynamics

Amniotic fluid at gestational age t (weeks) is under normal conditions generated by fetal urine flow and lung liquid secretion, and removed by fetal swallowing and intramembranous flow. For the latter flow (see Umur, van Gemert, & Ross, 2001), we have assumed that only free water moves across the intramembranous pathway into the fetal blood that perfuses the surface of the fetal side of the placenta, the fetal skin and the umbilical cord surface (e.g., Ross & Brace, 2001). However, from the moment of acardiac onset, the lack of a functioning heart induces hypoxic/ischemic damage of, among others, lungs and brain resulting in partial or complete loss of these organs. A damaged brain causes the disappearance of swallowing and diaphragmatic movements, so we excluded the possibility that remaining lung secretion and swallowing could affect acardiac growth and amniotic fluid dynamics. Thus, for the acardiac bodies with renal tissue considered here, only urine production, $U_{Ac}(t)$, produces amniotic fluid volume, $V_{Amn}^{Ac}(t)$, while intramembranous flow, $IM_{Ac}(t)$, removes it. Then,

$$\frac{dV_{Amn}^{Ac}(t)}{dt} = U_{Ac}(t) - IM_{Ac}(t) (\text{ml/week}) \quad (1)$$

In Appendix A, we derive that the intramembranous flow in an acardiac twin amniotic sac can be neglected compared to urine flow, implying that Equation (1) becomes

$$\frac{dV_{Amn}^{Ac}(t)}{dt} \approx U_{Ac}(t) \quad (2)$$

As before (Umur et al., 2001), we hypothesized that polyhydramnios implies about twice the normal amniotic fluid volume.

2.3 | Acardiac urine production dynamics

We assumed that the acardiac fetus has normal renal tissue and kidney function, which extends from 11 weeks

on, when urine flow becomes possible (Abramovich, 1968), to at least 10 weeks after acardiac onset (from pathology, PGJN). Its urine production, $U_{Ac}(t)$, versus mean arterial pressure in the aorta is obviously unknown too but, following Umur et al. (2001), Equations 3–5 below are from their Table 1, we assumed that urine production requires at least an incoming arterial pressure of half the normal value, $P_{aN}(t) = P_a^{Pu}(t)$, multiplied by pressure-diuresis function, $U_{pd}(P_a)$, and normal urine production, $U_N(t)$

$$U_{Ac}(t > 11) = U_N(t) \cdot U_{pd}(P_a) \ (\text{ml/week}) \quad (3)$$

$$U_N(t) = 24 \cdot 7 \cdot \left[10^{(0.088 + 0.041 \cdot t)} - 3\right] \ (\text{ml/week}) \quad (4)$$

$$U_{pd}(P_a) = \frac{10}{3} \cdot \left(\frac{P_a}{P_{aN}}\right)^2 - 3 \cdot \left(\frac{P_a}{P_{aN}}\right) + \left(\frac{2}{3}\right) \ (P_a > 0.5 \cdot P_{aN}) \quad (5)$$

From Figure 1, acardiac's mean arterial pressure, P_a^{Ac}, is the sum of the pump's venous pressure and the fraction of the acardiac- versus the (acardiac+AA)- resistances of the driving pressure source $\left(0.7 \cdot P_a^{Pu} - P_v^{Pu}\right)$. Thus ($R$ is resistance), and $P_a^{Ac} > 0.5 \cdot P_a^{Pu}$,

$$P_a^{Ac} = P_v^{Pu} + \frac{R_{Ac}}{R_{Ac} + R_{AA}} \cdot \left(0.7 \cdot P_a^{Pu} - P_v^{Pu}\right) > 0.5 \cdot P_a^{Pu} \quad (6)$$

Then, using that (van Gemert & Sterenborg, 1998)

$$P_a^{Pu} = 60 \cdot (t - 5)/35 \quad (7)$$

$$P_v^{Pu} = 7.5 \cdot (t - 5)/35 \quad (8)$$

gives, after canceling out the $(t - 5)/35$ terms, that

$$P_a^{Ac} = 7.5 + \frac{R_{Ac}}{R_{Ac} + R_{AA}} \cdot (0.7 \cdot 60 - 7.5) > 0.5 \cdot 60 \quad (9)$$

$$\frac{R_{Ac}}{R_{Ac} + R_{AA}} > \frac{(30 - 7.5)}{(42 - 7.5)} = 0.65 \quad (10)$$

In previous work (Ross, Ervin, Leake, Habeeb, & Fisher, 1986), ovine fetuses of 126 ± 3 days gestational age were made hypotensive during about 1 hr by intravenous infusion of nitroprusside. The measured urine production as a function of the mean arterial pressure is given in Figure 2. We fitted the measurements to the pressure-diuresis function of Equation (5), starting at the begin point of the linear trendline at 61 mmHg (blue dashed line), which gives that urine production requires

TABLE 1 Model outcomes. Urine production is assumed to start at 11 gestational weeks (Abramovich, 1968)

$r_{AA}(40)$ (mm)	a	CRL-ratio	t_{Ac} (wks)	UVD at t_{Ac}	UVF at t_{Ac}	GA poly (wks)
0.6	0.0029	0.143	10	6.71	302	14
	0.0031	0.146	11	6.37	272	14
	0.0043	0.163	12	5.69	184	14
0.8	0.0088	0.206	10	4.63	99.3	15
	0.011	0.222	11	4.22	75.2	15
	0.0138	0.24	12	3.88	58.4	15
1.0	0.019	0.267	10	3.74	52.3	13
	0.0235	0.286	11	3.27	35.0	13
	0.0335	0.322	12	2.91	24.6	13
1.3	0.061	0.394	10	2.48	15.3	13
	0.07	0.412	11	2.32	12.5	13
	0.118	0.456	12	2.00	8.00	13
1.8	0.175	0.559	10	1.79	5.74	15
	0.25	0.63	11	1.61	4.17	13–14
	0.26	0.638	12	1.57	3.87	13

Note: $r_{AA}(40)$: arterio-arterial anastomotic radius at 40 weeks, Equation (19); a: the acardiac/pump blood volumetric ratio at acardiac onset, Equation (12); CRL-ratio: the acardiac/pump crown-rump-length ratio defined as $a^{1/3}$, Equation (25); t_{Ac}: acardiac onset; UVD: umbilical venous diameter ratio; UVF: umbilical venous flow ratio; GA poly: the only gestational age where polyhydramnios is predicted to occur.
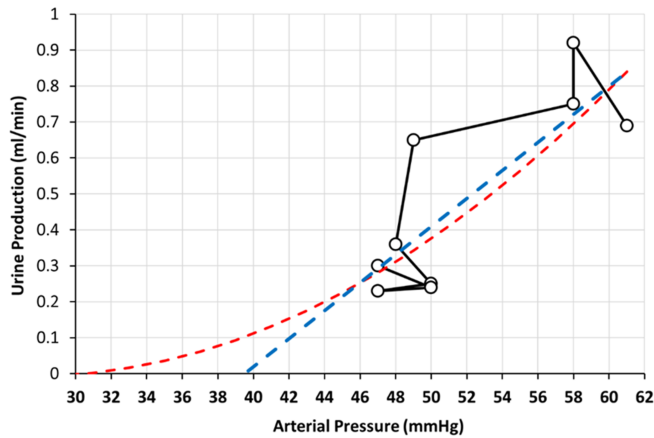

FIGURE 2 Arterial pressure and urine production measurements from 6 studies in 5 third trimester prepared fetal lambs at 126 ± 3 days gestation (term is 145–150 days) (Ross et al., 1986). Blue dashed line: linear trendline to define the beginning point (61,0.84) of the pressure-diuresis curve. Red dashed line: fit of the pressure-diuresis function $U_{pd}(P_a)$, Equation (5)

$P_a^{Ac} > 30/61 = 0.49 \cdot P_a^{Pu}$. Thus, we kept the factor of $P_a > 0.5 \cdot P_{aN}$ in Equation (5), as Umur et al. (2001) previously suggested. We neglected possible, albeit unknown, differences between urine production in an acute hypotensive ovine fetus and acardiac urine flow at chronically low perfusion pressure and hypoxemia.

Based on our assumptions that (a) acardiac kidney function remains normal during a period of 10 weeks after acardiac onset, (b) acardiac onset is before 13 weeks, and (c) urine production starts at 11 weeks (Abramovich, 1968), implies that an acardiac twin can produce urine for a significant period after 11 weeks, once its mean arterial pressure is at least half the pump's mean arterial pressure.

2.4 | Pump and acardiac development

As previously (van Gemert & Sterenborg, 1998), the pump's blood volume, $V_{Pu}(t)$ (ml), follows from the normal monochorionic twin fetal blood volume as

$$V_{Pu}(t) = V_N(t) = 149 \cdot (t/31)^3 \tag{11}$$

which holds until 31 weeks, long enough for the present analysis. In some cases below, for example, case 10, we know the pump's weight at birth. Then, we use that the pump's blood volume is 10% of its weight, and rather than using the 149-term, we fit this term to the known blood volume while keeping the $(t/31)^3$ dependency.

At acardiac onset, t_{Ac} (weeks), we use, as previously (van Gemert et al., 2017), that the acardiac blood volume, $V_{Ac}(t_{Ac})$, is a factor of $a < 1$ times the pump's blood volume, thus

$$V_{Ac}(t_{Ac}) = a \cdot V_{Pu}(t_{Ac}) \tag{12}$$

In previous work (van Gemert, Ross, et al., 2016), we assumed that acardiac growth, dV_{Ac}/dt, was the product of the acardiac perfusion flow, $F_{Ac}(t)$, and the ratio of normal fetal growth, dV_N/dt, and normal fetal perfusion, $F_N(t)$, thus

$$\frac{dV_{Ac}(t)}{dt} = \frac{F_{Ac}(t)}{F_N(t)} \cdot \frac{dV_N(t)}{dt} \qquad (13)$$

where, Equation (11),

$$\frac{dV_N(t)}{dt} = \frac{dV_{Pu}(t)}{dt} = \frac{3 \cdot 149}{(31)^3} \cdot t^2 = 0.015 \cdot t^2 \qquad (14)$$

However, when simulating one of the cases (case 20, see below), with knowledge of the acardiac weight at birth, these relations simulated a too small acardiac blood volume. To compensate for that, we had to increase the 0.015 to 0.024. Then, the integration of Equations (13) and (14), results in

$$V_{Ac}(t) = a \cdot V_{Pu}(t_{Ac}) + 0.024 \cdot \int_{t_{Ac}}^{t} \frac{F_{Ac}(x)}{F_{Pu}(x)} \cdot x^2 \cdot dx \qquad (15)$$

Finally, in case 10 below, modeling the known acardiac weight at 27.6 weeks required an additional increase in the acardiac growth rate by a factor of 1.5.

2.5 | Pressure and flow distribution along the resistance network

From Figure 1, it is straightforward to calculate the pressures and flows along the resistance network. First, the resistance, R, "seen" by the pump twin is the sum of the pump's umbilical arterial resistance, R_{ua}^{Pu}, and the parallel resistance of the pump's placenta, R_{Pl}, and the sum of the acardiac and AA resistances $(R_{Ac} + R_{AA})$, or

$$R = R_{ua}^{Pu} + \frac{R_{Pl} \cdot (R_{Ac} + R_{AA})}{(R_{Pl} + R_{Ac} + R_{AA})} \qquad (16)$$

The total flow produced by the pump twin then is

$$F_{Pu} = \left(P_a^{Pu} - P_v^{Pu}\right)/R \qquad (17)$$

Second, the incoming arterial pressure of the acardiac body, P_a^{Ac}, and the acardiac perfusion flow, F_{Ac}, are respectively

$$P_a^{Ac} = \left(0.7 \cdot P_a^{Pu} - P_v^{Pu}\right) \cdot \frac{R_{Ac}}{(R_{Ac} + R_{AA})} \qquad (18)$$

$$F_{Ac} = \frac{\left(0.7 \cdot P_a^{Pu} - P_v^{Pu}\right)}{(R_{Ac} + R_{AA})} \qquad (19)$$

Relations of the resistances are summarized in Appendix B.

2.6 | Analysis of our seven acardiac twins with one or two kidneys

From Maroun and Graem (2005), the measured acardiac body weight, crown-rump, crown-heel and foot lengths can estimate the age of acardiac maturation at birth. Then, again from Maroun and Graem (2005), we assumed that the pump twin's weight at that age follows from their tabulated mean weights. Arbitrarily, acardiac onset was assumed at 9 weeks. However, also simulating onset at 10–12 weeks showed no significant different model outcomes (see also Table 1). When the value of a was unknown, and a reasonable guess impossible, we assumed that a also = 0.2 may be a pragmatic choice, somewhat arbitrarily derived from the average ratio of pump-to-acardiac Crown-Rump-Length (CRL) data by Lewi et al. (2010) (see third paragraph of Study Limitations), and using

$$a \approx CRL^3 \qquad (20)$$

(van Gemert et al., 2017, Equation (11)). From the available acardiac information, we adjusted the $r_{AA}(40)$-value to obtain the acardiac blood volume. We then predicted whether polyhydramnios would have occurred and, if so, from what gestational age on. Below (Results, Acardiac Pathology Data), we give details of the two previously described cases 20 and 10 where the UVD-ratios were known (van Gemert et al., 2016).

3 | RESULTS

3.1 | General

Table 1 summarizes the largest a also-value, corresponding CRL-ratio, $r_{AA}(40)$-value, and acardiac onset age, that model polyhydramnios occurring at the gestational age mentioned, but neither before nor after that gestational age (see Figure 3, case $a = 0.061$). These outcomes imply that polyhydramnios occurs over a longer gestational age period at all lower a-values and that it does not occur at all larger a-values (e.g., Figure 3). Noteworthy is that the acardiac bodies are relatively small and that an assumed acardiac onset at 10–12 weeks does not make much of a difference.

3.2 | Acardiac pathology data

In our own pathology program (PGJN), we collected 18 acardiac twins from 1997 onward. From these 18 acardiacs, 7 (39%) were found to have one or two
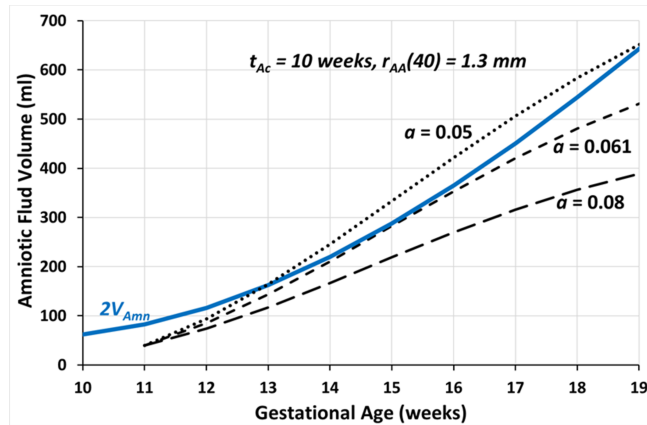

FIGURE 3 Three examples of amniotic fluid predictions using acardiac onset at 10 weeks and $r_{AA}(40)$ of 1.3 mm, versus twice the normal amniotic fluid volume, the criterion used for polyhydramnios. The example of $a = 0.061$ (CRL-ratio 0.394), mentioned in Table 1, gives polyhydramnios at 15 weeks only. A larger $a = 0.08$ (CRL-ratio 0.43), will not produce polyhydramnios, the mean arterial pressure remains lower that half the pump twin's value. A smaller $a = 0.05$ (CRL-ratio 0.368) gives polyhydramnios over a larger age period than only 15 weeks, here between 13 and >19 weeks

kidneys. None was reported to develop polyhydramnios. However, 4 of these 7 cases were lasered at gestational ages of respectively 14.6, 16, 20 and 27.6 weeks with intrauterine pump twin demise soon thereafter, 1 other pregnancy had spontaneous intrauterine demise of the pump twin at 20 weeks, and the other 2 pregnancies were terminated. The data and model outcomes are summarized in Table 2. The last two of our laser cases, at 20 and 27.6 weeks, were described previously as cases 20 and 10 in Table 1 of van Gemert, Pistorius, et al. (2016).

In case 20 (S01-347), signs of pump twin decompensation resulted in laser coagulation of the acardiac's umbilical cord at 20 weeks. The UVD-ratio was 1.8. Birth was at 40.6 weeks and the acardiac body without a cranium weighted 45 g. Autopsy showed an acardiac maturation of 15–16 weeks. We used acardiac onset at 9 weeks, and an a of 0.2. Our model outcomes are summarized in Table 2. Polyhydramnios was correctly predicted not to occur.

Case 10 (S05-233) was a dichorionic-triamniotic triplet pregnancy with dichorionic monochorionic twins. The singleton triplet was observed to have demised at 10.6 weeks. A small structure was also vaguely seen which turned out later to be an acardiac twin. Due to significant growth of the acardiac body, elective laser therapy was applied at 27.6 weeks, resulting in pump twin exsanguination into the acardiac body. From Equation (3) of van Gemert, Ross, et al. (2016), the pump's excess cardiac output fraction follows from

TABLE 2 Model predictions of seven acardiac twins with one or two kidneys (PGJN). Diameter-ratio (equal to $a^{1/3}$) of $a = 0.2$ is 0.59, of $a = 0.3$ is 0.67 and of $a = 0.5$ is 0.79

Case	AcMat (AcOn)	Kdn	W_{Ac} (gr)	W_{Pu} (gr)	a	UVD (meas/mod)	$r_{AA}(40)$ (mm)	Poly	Comment
S01-347	15–16 (9)	1	45	≈95[#]	0.2	1.8/1.84	0.95	No	Case 20; laser at 20 wks; birth at 40.6 wks
S02-045	12 (9)	1	14.5	54	0.2	3.19	0.61	No	IUFD at 20 wks
S04-320	12 (9)	2	9.3	24.5	0.2	2.67	0.81	No	Laser at 14.6 wks; IUFD 15.6 wks; birth 19.4 wks
S05-233	16–20 (9)	2	326	1,090	0.3	4.7/2.05	0.75	No	Case 10; laser at 27.6 wks; IUFD at 28 wks
S08-033	12 (9)	2	37.4	350	0.2	2.1	0.88	No	Laser at 16 wks; IUFD at 15.8 wks
S16-027	10 (9)	1	4.7	11.6	0.5	3.1	0.75	No	Monoamniotic twins at 11.7 wks terminated; acardiac with partial head and humeri.[#]
S18-061	10–11 (9)	1	2.9	16	0.2	4.2	0.54	No	Terminated at 14.4 wks

Note: AcMat: acardiac maturation (wks); AcOn: acardiac onset used (wks); Kdn: kidney; W_{Ac}: acardiac weight (gr); W_{Pu}: pump weight (gr); a: estimated blood volumetric ratio of acardiacus and pump twin at acardiac onset used in the model; $r_{AA}(40)$ (mm): radius of the AA anastomosis at 40 weeks, see Equation (19); UVD(meas/mod): UmbilicalVenousDiameter ratio (measured/modeled); Poly: polyhydramnios; [#]Estimated from crown-rump, crown-heel and foot lengths (Maroun & Graem, 2005). [#]Figure 7 of van Gemert et al. (2017).

$$PumpExcessFractCO = \frac{F_{Ac}}{(10/3) \cdot F_{Pu}} = \frac{0.3}{(UVD-ratio)^3 - 1}$$

$$(21)$$

where $(UVD - ratio)^3 = (UVF - ratio)$, UVD is Umbilical Venous Diameter, UVF is Umbilical Venous Flow. The reported UVD-value of 4.7, measured from a pathology slide at 28 weeks, implies that the pump twin had to increase its cardiac output by only 0.3%, which could neither have caused the growth of this acardiac twin nor the pump's IUFD. Pump and acardiac weights at autopsy were 1,090 and 326 g. However, exsanguination occurred following laser therapy, the cause of the pump's IUFD. Assuming that about 50% of the pump's blood exsanguinated into the acardiac body, or about 55 mL, the pump thus weighted about 1,150 g and the acardiac about 270 g. Then, assuming that pump blood volumetric growth remains proportional to $(t/31)^3$, we have at $t = 27.6$ weeks that $V_{Pu}(t) \approx 163 \cdot (t/31)^3$. Unfortunately, the placenta was fragmented and no anastomoses were identifiable. The whole placental parenchyma showed hydropic changes, thus hypoxemia in both fetuses, signs of a strongly increased blood production and a longer existing intrauterine demise. The acardiac umbilical cord showed 3 vessels. Crown-rump, crown-heel, and foot lengths, of respectively 14, 21 and 3 cm, are indicative of a maturation between 16 and 20 weeks (Maroun & Graem, 2005). However, acardiac onset was obviously earlier, with an unknown blood volumetric ratio. We used $a = 0.3$ and acardiac onset at 9 weeks. The model outcomes are given in Table 2. Polyhydramnios was predicted not to occur. We hypothesized that a stenosis in the venous return must have occurred here because then the umbilical venous flow ratio would not be given by the UVD-ratio to the third power and could imply a much larger perfusion flow to the acardiac. As the most likely option, we consider that the stenosis is located in the VV on the placenta.

Figure 6 in previous work (van Gemert et al., 2017) gives the ultrasound picture of the pump and acardiac twins at 7 weeks, with a estimated as 0.16 (CRL-ratio 0.54), acardiac onset at 6 weeks, and $r_{AA}(40)$ (arbitrarily) as 1.3 mm. No kidney information was available here; however, we assume that one or two kidneys could have been present. The previously mentioned $r_{AA}(40) = 2.05$ mm (van Gemert et al., 2017) would produce an unrealistically large acardiac body. The model then gives that UVD(6wks) = 3.3, implying that this pregnancy was at risk for adverse outcome of the pump (e.g., Figure 3 of van Gemert et al., 2017), which actually happened (at 31 weeks, a long standing IUFD was observed), but that polyhydramnios would not have developed.

4 | DISCUSSION

The most important and novel outcome of our modeling is that acardiac twins with normal urine flow will produce polyhydramnios once their mean arterial pressure is large enough, at least half the pump twin's value, and persists long enough. Of note, intramembranous flow plays no significant role in the removal of acardiac sac amniotic fluid to control the significantly larger urine flow (Appendix A).

The association of urine flow with arterial pressure requires reasonable validity of the pressure-diuresis relation, Equation (5). In our model, polyhydramnios can develop at all $r_{AA}(40)$-values considered (Table 1). We used mean arterial and venous blood pressures as derived before (van Gemert & Sterenborg, 1998), however, we emphasize that the absolute pressures do not influence our findings because the pressure-diuresis curve of Equation (5) is based on *relative* arterial pressure values. We also found that an acardiac mean arterial pressure of at least half the pump's value requires a larger acardiac than AA vascular resistance, actually, from Equation (10), by a factor of $R_{Ac}/R_{AA} > 1.86$. Thus, a larger acardiac body (larger a-value, lower acardiac resistance) requires a larger diameter AA anastomosis (lower AA resistance) to be able to produce urine flow.

We postulate that cases of the acardiac twin having renal tissue but without polyhydramnios is likely a result of markedly low blood pressure and thus insufficient renal perfusion pressure to produce urine. Furthermore, the likely etiology of the acardiac twin lacking renal tissue is a further reduction in blood pressure resulting in renal agenesis.

When the acardiac's mean arterial pressure at 11 weeks is at least half the pump's value, urine production is assumed to start. We also assumed that the amniotic fluid volume then is the normal value of 40 ml (Umur et al., 2001), hence polyhydramnios at twice the normal amniotic fluid volume needs time to develop. During that time period, the acardiac's mean arterial pressure needs to remain above half the pump's value, requiring that $R_{Ac}/R_{AA} > 1.86$ (previous paragraph). Thus, our growth mechanisms assumed for acardiac body and AA anastomosis affect our predictions of excess amniotic fluid development. We used that growth of the AA is inversely proportional to the third power of $(t$-4), Equation (B4) in Appendix B. However, growth of the acardiac mean arterial pressure is much more

complicated as it involves acardiac and AA resistances, pump's arterial and venous pressures, and acardiac-AA blood flow. The model predicts that the acardiac mean arterial pressure decreases slowly with gestation.

Examples of long-term polyhydramnios are the case of $a = 0.05$ (CRL-ratio 0.37) in Figure 3, with predicted polyhydramnios from 13 to 19 weeks, and the case (not shown) of $a = 0.02$ (CRL-ratio 0.27) with polyhydramnios from 11.8 weeks on. Interestingly here, from 22 weeks on, the arterial pressure is below half the pump's value, so removal of excess acardiac sac amniotic fluid is then by the intramembranous flow. On the other hand, when the acardiac's mean arterial pressure at 11 weeks is marginally larger than half the pump's value, and decreases with gestation, urine flow may become inadequate for polyhydramnios onset. An interesting assumption then is that acardiac twins found without renal tissue had marginal or too low arterial pressure for urine production, because insufficient/no renal blood flow cannot maintain renal viability. From Healey's paper, $146/203 = 72\%$ acardiacs had renal tissue (Healey, 1994; Sato, Kaneko, Konuma, Sato, & Tamada, 1984), versus $7/18 = 39\%$ in our series.

Recently, Marella et al. (2015) reported a very interesting case of progressive polyhydramnios in the acardiac twin's sac toward 29 weeks. After amnioreduction (volume not reported), amniotic fluid reaccumulated, fetal heart rate abnormalities developed and at $33 + 1$ weeks a caesarian section delivered pump and acardiac twins of 1997 and 400 g. The pump's umbilical cord was inserted on the intertwin dividing membrane. The acardiac body lacked an umbilical cord and was directly attached to the placenta. A remarkable and unexplained finding was that the polyhydramnios could not have been of urinary origin because pathology showed no evidence of kidneys and bladder! Here, we assert that the acardiac body could have functioned as an exceedingly large placental chorangioma, based on a number of published cases where large chorangiomas caused polyhydramnios (e.g., Abdalla, Bachanek, Trojanowski, Cendrowski, & Sawicki, 2014). Unfortunately, this well-known complication has not yet been fully understood (e.g., Abdalla et al., 2014).

4.1 | Study limitations

First, the key limitation of our modeling obviously is that we have to deal with a significant number of unknowns. The two most important ones are that we basically know nothing of the pressure-diuresis curve following long-term underperfusion and low oxygen tension of the renal tissue. The other important unknown is the various growth mechanisms that create the four morphological forms of acardiac twins (Das, 1902), that is, about 5% is an acardius acormus (only facial structures), 8% an acardius anceps (with rudimentary cranial structures), 25% an acardius amorphous (no recognizable form present), and 62% an acardius acephalus (lacking cranial structures). Equally so, we do not usually know the gestational age of acardiac onset, the a-value at onset, and the dimensions of the AA anastomosis. The case of Figure 7 in previous work (last paragraph of Results; van Gemert et al., 2017) is an exception in that it provides several fetoplacental parameters that are commonly unknown. All these parameter uncertainties likely explain that we do not understand why 30 of 41 acardiac twins with renal tissue develop polyhydramnios (Healey, 1994). We assumed that the other 11 could not produce the value and/or duration of mean arterial pressure for urine flow required for polyhydramnios onset.

Second, we assumed the pump twin to be a healthy normal fetus throughout pregnancy, irrespective of possible acardiac influences, for example, hypoxemia. This assumption prevents knowing how acardiac polyhydramnios affects the pump twin's wellbeing compared with no acardiac polyhydramnios. We also assumed that the diameter and length of the AA anastomoses are not influenced by any changes that can occur in the acardiac body and hence in its resistance. And, from lack of knowledge, we derived the mean arterial blood pressure-diuresis function of Equation (5) from adult physiology (Umur et al., 2001).

Third, we have assumed that an acardiac twin whose mean arterial pressure exceeds half the pump's value produces normal fetal urine flow according to Equation (3). Yet, Table 1 shows that acardiac twins that produce polyhydramnios on that basis are relatively small, where a varies between 0.3% and 26%. In 24 first trimester diagnosed acardiac twins, Lewi et al. (2010) found an average pump crown-rump-length of 62 ± 8 mm and an average acardiac upper-pole-rump-length of 36 ± 12 mm, thus an average length ratio of $36/62 = 0.58$. The corresponding average a-value then is approximately given by the third power of 0.58, or $a \approx 0.2$, Equation (20). Despite the large uncertainty in this value, unknown because the 24 individual length-ratios were not provided, it nevertheless suggests that acardiac twins are usually larger than some of the modeled cases in Table 1. A remark here is that a "small" acardiac body will often be a "large" acardiac body with several organs missing, for example, head, liver and extremities. Further (Healey, 1994), we recall the significant association reported between the acardiac/pump birth weight ratio and polyhydramnios ($p = .036$), suggesting that larger acardiac bodies more often produced polyhydramnios than smaller bodies. In addition, we assumed that acardiac polyhydramnios requires an

acardiac sac amniotic fluid volume of twice the volume of a normal fetus. Yet, the clinical amniotic/fetal fluid volume ratio is at least about 2 for the first 15 gestational weeks, so smaller fetuses, including acardiac twins, have inherently a concomitantly smaller amniotic fluid volume. When this concept is applied for defining polyhydramnios as twice the *natural* small twin amniotic fluid volume, polyhydramnios is predicted to occur in all cases of Table 1. However, we recall that the clinical methods of polyhydramnios assessment were not provided.

Fourth, normal urine production requires filtration of blood by the glomeruli and back resorption of the filtrated fluid by the tubuli. Acardiac onset and perfusion by arterial blood of the pump twin both affect the oxygen level of the acardiac body and thus also of the tubuli. Particularly, the proximal tubuli are well-known to be sensitive for hypoxic damage, which may result in renal tubular dysgenesis, for example, as seen in twin-twin transfusion syndrome donors (Oberg, Pestaner, Bielamowicz, & Hawkins, 1999). We could not test this hypothesis in our series due to severe maceration of the acardiac fetuses. However, in case S18-061 (Table 2), we observed a discontinuous nephrogenic zone in the single kidney of the acardiac fetus. The pump twin had a congenital heart defect (Ventricle-Septum-Defect, pulmonary hypoplasia and right descending aorta). The kidneys of the pump twin had a normal aspect. The discontinuous nephrogenic zone in the acardiac twin might be due to hypoxic/ischemic injury. Damaged proximal tubuli cause an increased urine flow, which can result in polyuria. We hypothesize that this mechanism may be quite realistic in acardiac twins with renal tissue. It also suggests that acardiac urine flow measurements will resolve this part of the acardiac pathophysiology.

Finally, acardiac twinning in monochorionic twin pregnancies is exceedingly complex fetal pathophysiology, where the various mechanisms that result in their onset and development into the four bizarre forms of acardiac bodies (Das, 1902) are not understood at all. Thus, a model description of acardiac polyhydramnios can be considered as a bold endeavor. Therefore, like any other model, our model is a deliberate oversimplification of pathophysiology aimed to suggest possible mechanisms and measurements, for example, of urine production of an acardiac twin with renal tissue, that may lead to a better understanding of the reported facts.

In conclusion, our modeling assumed that acardiac twins with renal tissue produce urine flow from 11 weeks on once their mean arterial pressure exceeds half the pump's mean arterial pressure. Because acardiac urine flow dominates the intramembranous control flow, the model predicts that polyhydramnios will develop in the acardiac sac when urine is produced sufficiently long. One of the outcomes of our modeling, shown in Table 1, is that very small acardiac/pump ratios can produce polyhydramnios. We provided arguments that renal tubular dysgenesis is expected to occur too and hence acardiac polyuria is a realistic possibility. We therefore hypothesize that this mechanism of large urine flows could be the more likely explanation of the occurrence of acardiac polyhydramnios. Verification requires urine flow measurements in acardiac sacs.

Most importantly, these results suggest the potential for prediction of which clinical cases may or may not develop polyhydramnios based upon noninvasive assessments of renal tissue, blood flow and urine production. This information would be of great value in determining early obstetric interventions as opposed to conservative management.

CONFLICT OF INTEREST
The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available from the corresponding author upon reasonable request.

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APPENDIX A: ACARDIAC SAC INTRAMEMBRANOUS FLOW

The intramembranous flow in acardiac amniotic sacs will be (much) smaller than under normal conditions, because (a) the acardiac placenta is not perfused by the acardiac body anymore and thus does not contribute to acardiac intramembranous flow (van Gemert, Ross, et al., 2016), and (b) the acardiac body is usually (much) smaller than the body of the pump twin, we used factor a for the ratio between acardiac and normal body volume, Equation (12). Thus, very limited surface area for intramembranous amniotic fluid absorption remains.

Umur et al. (2001) expressed the intramembranous flow (in ml/week) as

$$IM(t) = SL_{IM}(t) \cdot [(P_{Am} - P_{Fet}) - 19.6 \cdot (Osm_{Am} - Osm_{Fet})] \quad (A1)$$

where the fetal capillary pressure, $P_{Fet} = P_v + (P_a - P_v)/3$, is added to the amniotic fluid pressure, thus $(P_{Am} - P_{Fet}) = (-P_{Fet})$. Further, $SL_{IM}(t)$ is the product of $S_{IM}(t)$, the combined total surface of the placenta (fetal side), fetal skin and umbilical cord as a function of gestation, and filtration coefficient $L_{IM}(t)$ (Umur et al., 2001). From Table 1, Eq. (m7) of Umur's paper, the following relation was used

$$SL_{IM}(t) = 7 \cdot (0.0588 \cdot t - 0.6596) \quad (\text{ml} \cdot \text{mmHg/week}) \quad (A2)$$

For acardiac twins, we have to adapt surface $S_{IM}(t)$, in Equation (A1) derived from an uncomplicated

pregnancy, by deleting the placental surface and replacing the normal fetal surface by the smaller acardiac surface. Using that the acardiac and the pump total body fluid (TBF) volumes are 10 times their blood volumes (Umur et al., 2001), and assuming for simplicity spherical shapes, gives that TBF relates to its radius as

$$TBF(t) = (4\pi/3) \cdot r^3 \qquad (A3)$$

Thus, solving for r and using that a spherical surface is given by $4\pi \cdot r^2$, and using Equation (A3), gives for the surface areas of the acardiac and normal pump twins that (in m²)

$$S_{Ac}(t) = 4\pi \cdot [(3/4\pi) \cdot a \cdot TBF_N(t)]^{2/3} \qquad (A4)$$

$$S_N(t) = 4\pi \cdot [(3/4\pi) \cdot TBF_N(t)]^{2/3} \qquad (A5)$$

The surface area (m²) used for a normal placenta is

$$S_{Pl}(t) = \pi \cdot (t/3.5)^2 \qquad (A6)$$

Thus, for acardiac amniotic sacs, we find

$$SL_{IM}^{Ac}(t) = 7 \cdot (0.0588 \cdot t - 0.6596) \cdot \frac{S_{Ac}(t)}{S_N(t) + S_{Pl}(t)} \qquad (A7)$$

$$IM_{Ac}(t) = SL_{IM}^{Ac}(t) \cdot \left[-\left\{ P_a^{Ac} + \frac{(P_a^{Ac} - P_v^{Pu})}{3} \right\} - 19.6 \cdot (Osm_{Am} - Osm_{Fet}) \right] \qquad (A8)$$

We used the osmolality values as tabulated in Table 2 of Umur et al. (2001). Because

$$\frac{S_{Ac}(t)}{S_N(t) + S_{Pl}(t)} = \frac{a^{2/3}}{1.091} \approx a^{2/3} \qquad (A9)$$

we have that,

$$IM_{Ac}(t) = \frac{a^{2/3}}{1.091} \cdot IM(t) \approx a^{2/3} \cdot IM(t) \qquad (A10)$$

where we neglected blood pressure differences. Table 1 shows the various largest modeled a-values that still produce polyhydramnios just at the aged mentioned, at the five $r_{AA}(40)$-values we used. Except for large a-values at $r_{AA}(40)$=1.8 mm, for example, 0.26 at 12 weeks assumed acardiac onset, which gives, $a^{2/3}$=0.407, all other cases produce much smaller $a^{2/3}$-values. Because normal urine flow up to 20 weeks is already 3 to 7 times larger than normal intramembranous flow (Table 2 of Umur et al., 2001), acardiac (normal assumed) urine flows are significantly larger than acardiac sac estimated intra-membranous flows.

APPENDIX B: RESISTANCE RELATIONS

As derived previously (Equations 2, 4, 6 and 7 of van Gemert, Ross, et al., 2016), the acardiac's vascular resistance is related to the acardiac's blood volume, V_{Ac} (ml), as

$$R_{Ac} = 0.00075/V_{Ac} \text{ mmHg}/(ml/week) \qquad (B1)$$

From previous work (Appendix A of van Gemert et al., 2017; van Gemert & Sterenborg, 1998), we summarize the following resistance relations (for the placenta, umbilical arteries and the AA anastomosis)

$$R_{Pl}(t) = \frac{0.41}{(t+5) \cdot (t^2 + 25)} \qquad (B2)$$

$$R_{ua}^{Pu}(t) = \frac{0.17}{(t+5) \cdot (t^2 + 25)} \qquad (B3)$$

$$R_{AA}(t) = \frac{8 \cdot 0.005}{\pi} \cdot \frac{0.075 \cdot (t-4)/(27 \cdot 1.193)}{[r_{AA}(40) \cdot (t-4)/(27 \cdot 1.193)]^4} \cdot \left(\frac{1}{1.3333 \cdot 10^8 \cdot 60 \cdot 60 \cdot 24 \cdot 7} \right) \qquad (B4)$$

We use $r_{AA}(40)$ as the AA-radius at 40 weeks, one of the input parameters in the model. The length of the AA anastomosis at 40 weeks has been taken here as 7.5 cm, half the value used previously, because of the hypertrophied acardiac placenta. The blood viscosity used as before is 0.005 N/(m·s²). The last term between brackets converts the SI value for resistance [(N/m²)/(m³/s)] to [mmHg/(ml/week)].