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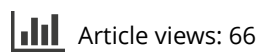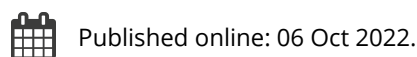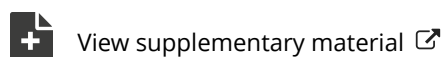
Impact of chemotherapy during pregnancy on fetal growth

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ABSTRACT

Background: Chemotherapy crosses the placenta, however, it remains unclear to what extent it affects fetal growth. The current literature suggests up to 21% of the offspring of women receiving chemotherapy are small for gestational age (SGA, birth weight <10th percentile). Limiting research to birth weights only might misjudge fetal growth restriction (FGR) in this high-risk population with multiple risk factors for impaired fetal growth. Moreover, the role of the duration of chemotherapy and gestational age at initiation of chemotherapy in fetal growth is yet poorly understood.

Objective: This retrospective cohort study evaluates fetal growth and neonatal birthweights in pregnant women receiving chemotherapy.

Study design: All pregnant patients, registered by the International Network of Cancer, Infertility and Pregnancy (INCIP), treated with chemotherapy with at least two ultrasounds reporting on fetal growth, were eligible for this study. Duration and gestational age at initiation of chemotherapy were our major determinants, followed by cancer type and stage, maternal characteristics (parity, BMI, ethnicity hypertension, and diabetes) and individual cytotoxic agents (anthracycline, taxanes, and platinum). Fetal growth outcomes were described using the following mutually exclusive groups (1) FGR, based on a Delphi consensus (2016); (2) "low risk SGA" (birth weight below the 10th percentile), but an estimated growth above the 10th percentile; (3) "fetal growth disturbance", which did not meet all FGR criteria; (4) "non-FGR". Obstetric and oncological characteristics were compared between the growth impaired groups and non-FGR group. We calculated estimated fetal weight (EFW) according to Hadlock's formula (1991) and birth weight percentile according to Nicolaides (2018). We used univariable and multivariable regression, and linear mixed effect models to investigate the effect of duration and gestational age at initiation of chemotherapy on birth weight, and fetal growth, respectively.

Results: We included 201 patients, diagnosed with cancer between March 2000 and March 2020. Most patients were diagnosed with breast cancer ($n = 132$, 66%). Regimens included anthracyclines ($n = 121$, 60%), (anthracyclines and) taxanes ($n = 45$, 22%) and platinum ($n = 35$, 17%). Fetal growth abnormalities were detected in 75 pregnancies: 43 (21%) FGR, 10 (5%) low risk SGA and 22 (8.5%) fetal growth disturbance. Chemotherapy prior to 20 weeks of gestation (47% vs. 25%, $p = .04$) and poor maternal gestational weight gain (median percentile 15 (range 0–97) vs. 8 (0–84), $p = .03$) were more frequent in the FGR group compared to the non-FGR

group, whereas no difference was seen for specific chemotherapy or cancer types. Univariable regression identified gestational weight gain, hypertension, systemic disease, parity, neonatal sex and maternal BMI as confounders for birth weight percentiles. Multivariable regression revealed that each additional week of chemotherapy was associated with lower birth weight percentiles (–1.06; 95%CI −2.01; −0.04; $p = .04$), and that later initiation of chemotherapy was associated with an increase in birth weight percentile (1.10 per week; 95%CI 0.26; 1.95; $p = .01$). Each additional week of chemotherapy was associated with lower EFW and abdominal circumference (AC) percentiles (–1.77; 95%CI −2.21; −1.34, $p < .001$; −1.64; 95%CI −1.96; −1.32, $p < .001$, respectively).

Conclusions: This study demonstrates that FGR is common after chemotherapy in pregnancy, and that the duration of chemotherapy has a negative impact. Sonographic follow-up of fetal growth and well-being is recommended.

Introduction

When cancer is diagnosed during pregnancy, treatment should adhere as much as possible to standard recommendations for non-pregnant patients, including the administration of chemotherapy [1,2]. Chemotherapy has the potential to influence fetal development and growth directly by crossing the placenta [3]. Hence, cytotoxic agents should be avoided during the period of fetal organogenesis [3]. Indirect adverse effects of chemotherapy can be mediated by secondary poor maternal nutrition, hematological toxicity, and impaired placental function [4]. The largest cohort study to date on pregnant patients with cancer revealed a high occurrence (21%) of small for gestational age (SGA), defined as a birth weight below the 10th percentile, and antenatal chemotherapy was one of the risk factors [5]. SGA is often used as a proxy for fetal growth restriction (FGR). FGR is defined as a fetus that does not reach the intrinsic growth potential and is diagnosed based on specific ultrasound criteria [6]. Distinction between SGA and FGR is important as FGR represents pathological growth with the highest associated perinatal morbidity and mortality [6,7]. Moreover, the definition of SGA includes constitutionally healthy SGA fetuses with normal outcomes, however, misses growth impaired fetuses with a birth weight within normal limits [8].

The literature on fetal growth abnormalities related to chemotherapy has several limitations. Cancer and pregnancy rarely coincide, occurring in approximately one per 1000 pregnancies, which complicates conduction of prospective studies [9]. As preterm delivery for oncological reasons is common and impaired fetal growth may only occur in the third trimester of pregnancy, the exact incidence of chemotherapy-related FGR might be underestimated. Second, SGA does not properly represent FGR, as mentioned above. Third, besides antenatal chemotherapy, multiple other morbidities in the pregnant cancer population, such as high maternal age, stage of disease, nutritional status, co-medications, and cancer-related stress might negatively impact fetal growth [10]. Additionally, cancer patients usually receive multiple agents, complicating the interpretation of single agents effects.

The primary aim of this cohort study was to assess fetal growth and the occurrence of FGR in pregnancies exposed to chemotherapy for cancer, who were registered by the International Network of Cancer, Infertility and Pregnancy (INCIP) [11]. Additionally, the impact of the duration and the gestational age at initiation of chemotherapy, as well as the impact of specific cytotoxic agents and cancer characteristics, on neonatal birth weight was investigated.

Materials and methods

Data collection and inclusions

In 2005, INCIP initiated a registry of retro- and prospectively collected oncological and obstetric data of premenopausal women with cancer (Clinicaltrials.gov, number NTC00330447). This study was approved by the Ethical Committee of University Hospital Leuven (Belgian number B322201421061) and local approval was obtained from participating centers when indicated. From the INCIP database, all singleton pregnancies with antenatal chemotherapy and prenatal scan information were selected. Available prenatal scans (range 22–37 weeks of gestational age) were allocated according to the gestational age at execution: "24 weeks" (between 154 and 195 days) and/or "30 weeks" (between 196 and 230 days) and/or "34 weeks" (between 231 and 264 days). Only women with available scans belonging to two different interval groups, with an interval of at least two weeks, were eligible for the study. Cases with major neonatal congenital malformations were excluded. Obstetric and oncological data were collected.

Data processing and definitions

Systemic disease was defined as metastatic or stage IV disease, defined by TNM (T describes tumor size, N describes lymph node involvement, and M describes distant metastasis) or FIGO (the Federation of Gynecology and Obstetrics; stage IV for gynecological cancers includes tumor spread to adjacent pelvic or distant organs) staging systems, as well as locally advanced disease with organ dysfunction [12]. Duration of antenatal chemotherapy was defined as the interval between the first exposure and the last exposure during pregnancy, adding the duration of one chemotherapy cycle or the duration from last exposure to birth if the patient delivered earlier. Maternal weight gain was expressed in percentiles, according to the reference range for gestational age at delivery and pre-pregnancy BMI in a low risk pregnant population reported by Santos et al. [13].

The percentiles for measurements of fetal head circumference (HC), abdominal circumference (AC), and femur length (FL) were assessed by the reference range for gestational age of Snijders and Nicolaides [14]. The EFW from each examination was derived from Hadlock's formula, based on HC, AC, and FL [15]. EFW and birth weight by gestational age were expressed as crude percentiles, reported by the Fetal Medicine Foundation [16]. We used this international reference chart as it was designed to overcome the problem of underestimation of FGR in preterm birth, by providing information at all gestational ages, including babies *in utero*. If neonates had a birth weight below the 10th customized percentile, they were defined as SGA. Customized percentiles were calculated for birth weight, corrected for gestational age, ethnicity, neonatal sex, maternal pre-pregnancy BMI and parity [17]. Placental weight was corrected for gestational age at delivery [18]. Abnormal Doppler measurements were defined as pulsatility index (PI) of the umbilical artery >95th percentile according to the references by the Fetal Medicine Foundation [19]. The cerebroplacental ratio is defined as the ratio of the middle cerebral artery PI to the umbilical artery PI and assumed abnormal when <5th percentile [19].

Based on ultrasonographic features and birth weight, pregnancies were allocated into four mutually exclusive groups according to fetal growth impact:

1. FGR based on birth weight percentile below the 3rd percentile or ultrasonographic features defined by a Delphi consensus in 2016 (*the FGR group*) [6,20]. FGR before 32 weeks (early FGR) was defined as an AC or EFW percentile below the 3rd percentile or absence of end-diastolic umbilical flow or AC/EFW below the 10th centile in combination with abnormal Dopplers of the uterine artery or the umbilical artery (above the 95th percentile). FGR after 32 weeks (late FGR) was defined as AC/EFW below the 3rd percentile or at least two out of three of the following; EFW below the 10th percentile, AC/EFW crossing $\geq$50 growth percentiles and/or cerebroplacental ratio below 5th percentile and/or Doppler of umbilical artery above the 95th percentile. Asymmetrical FGR was defined by an HC/AC ratio greater than the 95th percentile [14].

Due to the inherent poor predictive value of ultrasound, a second group and a third group "at risk" were defined.

1. A second group included cases with a birth weight percentile below the 10th percentile, that otherwise did not meet any of the criteria for FGR (the "low risk SGA" group).
2. A third category "at risk" for fetal growth impact was defined when only one of the following features was present at the prenatal ultrasound: a decrease in AC/EFW of $\geq$50 centiles during the course of pregnancy or EFW/AC percentile below the 10th percentile (the "fetal growth disturbance" group).
3. The fourth category included all cases without growth abnormalities (the "normal fetal growth" group).

Statistical analyses

Descriptive statistics are presented as frequencies with percentages for categorical variables, or median with range and interquartile range for continuous variables. Oncological features and obstetric outcomes were compared between pregnancies with growth impact (FGR, "low risk SGA group", "fetal growth disturbance") and pregnancies without (non-FGR), using Chi-square for categorical variables or Fisher's exact test in case of frequencies lower than five, and Mann–Whitney's *U*-test for continuous variables. Multivariable linear regression models were used to evaluate the effect of duration of antenatal chemotherapy and gestational age at initiation on fetal growth and crude birth weight percentile. Confounders were included in the models if they showed an association with birth weight percentiles in the univariable analysis (*p* value <.2) or were well-established research-based

confounders for fetal growth or risk factors for SGA [5,21]. As the effect of gestational age at initiation of chemotherapy and duration of chemotherapy exposure are highly correlated, both variables were not used in one model. A linear mixed effects (LME) model for repeated measures was used to test whether duration of chemotherapy during pregnancy or gestational age at initiation of chemotherapy, together or separate, significantly explained the individual variability of each ultrasound measurement (EFW, AC, HC, and FL) [22]. All tests were two-sided, and a p value below .05 was assumed statistical significant for all tests. Analyses were performed using SAS software (version 9.4 of the SAS System for Windows, Cary, NC) and R (version 3.6.0) (R Foundation for Statistical Computing, Vienna, Austria).

Results

Study population

Out of 1008 pregnancies with antenatal chemotherapy registered in the INCIP database, 201 women were eligible (Supplementary Figure 1). The birth weight percentiles in this series were not significantly different from other registered INCIP cases ($n = 807$) treated with antenatal chemotherapy without available prenatal scan information (Supplementary Table 3). Most women were diagnosed with breast cancer (132, 66%) and anthracyclines were the most frequently administered chemotherapeutic agent (158, 79%) (Tables 1a and 1b). Overall, sonographic percentiles of EFW, HC, AC, and FL showed a decreasing trend, when comparing 24, 30, and 34-weeks scan results in 107 cases with ultrasounds at all of these timepoints (Supplementary Figure 2). However, boxplots of these measurements revealed a stable, wide range from percentile 0 to 100 (Supplementary Figure 2). Of note, 76 of 107 women (71%) had already initiated chemotherapy by the 24-weeks scan. The median birth weight percentile for the INCIP population was 30 (range 1–100) (Figure 1).

Out of 201 cases, 43 patients (21%) delivered an SGA neonate. In total, 75 of 201 (37%) pregnancies were subject to impaired fetal growth according to the predefined definitions: (1) FGR occurred in 43 fetuses (21%). In the FGR group, early FGR (<32 weeks of gestation) occurred in 19/43 (44%) fetuses and 7/43 (16%) FGR fetuses were classified as asymmetrical FGR. In addition, (2) 10/201 neonates (5%) were *low risk SGA* at birth and (3) 22/201 fetuses (17%) were *presumably FGR*. There was one stillbirth at 31 weeks of a fetus that was early (symmetrical) FGR based on

Table 1a. Characteristics (continuous variables) by groups.

	Total	Non-FGR	p Value	FGR	p Value	Low risk SGA	p Value	Fetal growth disturbance	p Value
Total N	201	126		43		10		22	
For maternal BMI at booking	170	106		38		8		18	
For maternal weight gain	151	83		33		8		17	
For placenta weight and percentile	176	91		27		7		16	
Maternal age at diagnosis (years)	33 (33–19; 46)	34 (21–45; 6)	.598	33 (24–46; 8)	.254	33 (24–43; 10)	.280	33 (19–41; 7)	
Maternal BMI at booking (kg/m²)	24 (16–42; 7)	25 (18–42; 7)	.021	22 (16–38; 5.9)	.263	24 (19–28; 4)	.927	25 (19–33; 3)	
Gestational weight gain (kg)	7 (−9 to 25; 6)	7 (−7 to 25; 7)	.085	5.9 (−9 to 18; 5)	.820	8 (2–22; 4)	.473	7 (1–16; 6)	
Maternal weight gain (percentile) (Santos)[a]	13 (0–97; 32)	15 (0–97; 37)	.033	8 (0–84; 28)	.197	7 (0–96; 21)	.473	10 (1–74; 27)	
GA chemo initiation (weeks)	22 (12–34; 9)	23 (12–34; 8)	.042	20 (13–32; 10)	.004	17 (16–22; 5)	.325	22 (12–33; 10)	
Duration of chemo during pregnancy (weeks)	12.3 (2–26; 7)	2 (2–26; 7)	.560	12 (3–22; 8)	.026	16 (7–20; 5)	.284	14 (3–24; 9)	
Number of courses of chemotherapy	5 (1–16; 3)	4 (1–16; 3)	.715	4 (1–16; 4)	.002	7 (5–12; 7)	.134	6 (1–16; 6)	
GA delivery (weeks)	37 (29–40; 3)	37 (31–40; 2)	.046	36 (29–39; 3)	.393	38 (35–39; 2)	.499	37 (33–40; 3)	
Crude birthweight percentile	30 (1–100; 46)	47 (10–100; 52)	<.001	3 (1–39; 14)	<.001	7 (3–9; 5)	.002	28 (10–90; 23)	
Customized birth weight percentile[b]	32 (0–99; 47)	46 (4–100; 44)	<.001	4 (0–41; 16)	<.001	8 (3–17; 9)	.032	25 (11–91; 32)	
Placental weight (g)[c]	394 (136–750; 158)	435 (243–750; 166)	<.001	308 (136–574; 113)	.008	294 (199–421; 157)	.546	391 (332–750; 103)	
Placenta percentile (Thompson)	4 (2–85;13)	8 (2–80; 27)	.004	2 (2–31; 3.3)	.214	2 (2–3; 0)	.498	5 (2–85; 11.3)	

BMI: body mass index; GA: gestational age.
The characteristics of the fetal growth restricted (FGR) group, "low risk SGA" group and "fetal growth disturbance" group are compared to the group with normal fetal growth (non-FGR). For all characteristics, the median (range; interquartile range) are given.
[a]According to the reference range for gestational age at delivery and pre-pregnancy BMI in a low risk pregnant population as reported by Santos et al.
[b]According to the reference chart reported by Gardosi et al.
[c]The INCIP database does not distinct between placental weight based on untrimmed or trimmed measurements, nor fixed or fresh.

Table 1b. Characteristics (categorical variables) by groups.

	Total		Non-FGR		FGR			Low risk SGA			Fetal growth disturbance		
	201		126		43			10			22		
Total N	N	%	N	%	N	%	p Value	N	%	p Value	N	%	p Value
Cancer type							.847			.287			.265
Breast cancer	132	66	81	64	29	67		7	70		15	68	
Gynecological cancer	23	11	18	14	5	12		0	0		0	0	
Hematological cancer	39	19	3	2	2	5		1	10		1	5	
Other	7	3	24	19	7	16		2	20		6	27	
US available							.503			.894			.027
All echo (24–30–34)	107	53	60	48	5	58		5	50		18	82	
Echo 24–30	53	26	35	28	11	26		3	30		3	14	
Echo 30–34	33	16	21	17	6	14		2	20		1	5	
Echo 24 and 34	11	5	10	8	1	2		0	0		0	0	
Ethnicity							.623			1			.746
Caucasian	175	87	108	85	39	91		9	90		19	86	
African	4	2	4	3	0	0		0	0		0	0	
Asian	20	10	12	10	4	9		1	10		3	14	
Other (including Hispanic)	2	1	2	2	0	0		0	0		0	0	
GA initiation chemo							.036			.011			.32
<20	68	34	32	25	20	47		7	70		9	41	
20–27.9	92	46	65	51	16	37		3	30		8	36	
≥28 weeks	41	20	29	23	7	16		0	0		5	23	
GA initiation chemo							.222			.005			.198
<16	25	12	12	10	8	19		0	0		5	23	
16–19.9	43	21	20	16	12	28		7	70		4	18	
20–23.9	55	27	38	30	10	23		3	30		4	18	
24–27	37	18	27	21	6	14		0	0		4	18	
28–31.9	30	15	23	18	5	11		0	0		2	9	
>32	11	5	6	5	2	5		0	0		3	14	
Maternal BMI							.03			.321			.686
<18.5	4	2	1	1	3	7		0	0		0	0	
18.5–24.9	91	45	52	41	24	56		6	60		9	41	
25.0–29.9	47	23	32	25	6	14		2	20		7	31	
>30.0	28	14	21	17	5	12		0	0		2	9	
Not reported	31	15	20	16	5	12		2	20		4	18	
Parity							.278			.091			1.000
Nulliparous	85	42	49	39	21	49		7	70		8	36	
Multiparous	115	57	77	61	21	49		3	30		14	64	
Not reported	1	1	0	0	1	2		0	0		0	0	
Smoking or substance use							1			.623			1.000
No	117	58	76	60	22	51		5	50		4	18	
Yes	30	15	18	14	6	14		2	20		14	64	
Unknown	54	27	32	25	15	35		3	30		4	18	
Hypertensive disorder							.16			1			1.000
No	198	99	125	99	73	95		10	100		22	100	
Yes	3	1	1	2	2	5		0	0		0	0	
Disease extent							.094			.604			.241
Local	178	89	115	91	35	81		10	100		18	82	
Systemic	23	11	11	9	8	19		0	0		4	18	
Diabetes							.204			1			.592
No	195	97	120	95	43	100		10	100		22	100	
Yes	6	3	6	5	0	0		0	0		0	0	
Treatment							.103			.239			.563
Anthracyclines	121	60	80	65	21	49		5	50		15	68	
(Anthracyclines +) taxanes[a]	45	22	22	17	14	32		4	40		5	23	
Platinum-based	35	17	24	19	8	19		1	10		2	9	
Anthracyclines							.525			.227			.252
No	43	21	26	21	11	26		4	40		2	9	
Yes	158	79	100	79	32	74		6	60		22	91	
Taxanes							.812			1			.148
No	141	70	105	83	37	86		9	90		17	77	
Yes	60	30	21	17	6	14		1	10		5	23	
Platina							.713			1			.766
No	163	81	103	82	59	79		8	80		19	86	
Yes	38	19	23	18	16	21		2	20		3	14	
Antenatal surgery							.859			.187			.813
No	124	62	79	63	15	35		4	40		13	59	
Yes	77	38	47	37	28	65		6	60		9	41	
Antenatal radiotherapy							Na			.074			Na
No	200	100	126	100	43	100		9	90		22	100	
Yes	1	1	0	0	0	0		1	10		0	0	

(continued)

Table 1b. Continued.

Total N	Total N	Total %	Non-FGR N	Non-FGR %	FGR N	FGR %	p Value	Low risk SGA N	Low risk SGA %	p Value	Fetal growth disturbance N	Fetal growth disturbance %	p Value
	201		126		43			10			22		
Antenatal rituximab							.741			1			.357
No	188	94	117	93	39	39		10	100		22	100	
Yes	13	7	9	7	4	4		0	0		0	0	
NICU admission							.764			1			.695
No	129	64	115	91	38	88		9	90		21	95	
Yes	53	26	11	9	5	12		1	10		1	5	
Neonatal sex							.21			.317			.245
Male	90	45	59	47	17	40		3	30		8	36	
Female	101	50	61	48	25	58		6	60		14	63	
Not reported	10	5	6	5	1	2		1	10		0	0	
GA delivery							.003			.51			.554
<32 weeks	7	4	1	1	6	14		0	0		0	0	
32–34 weeks	17	9	11	9	4	9		0	0		2	9	
34–37 weeks	81	40	51	40	15	35		3	30		12	55	
>37 weeks	96	48	63	50	18	42		7	70		8	36	
Onset of labor							.194			.123			.118
Spontaneous	45	22	22	17	11	26		4	40		8	36	
IOL	79	39	50	40	19	44		3	30		7	32	
Elective CS	70	35	51	40	11	26		2	20		6	27	
Not reported	7	3	3	2	2	5		1	10		1	5	
Spontaneous preterm labor										1			.037
No	182	91	117	93	39	91	.813	9	90		17	77	
Yes	19	9	9	7	4	9		1	10		5	23	
Reason of IOL (n = 79)			N = 50		N = 19		.229	N = 3		1	N = 7		.936
Maternal obstetrical	4	5	2	4	2	11		0	0		0	0	
Fetal obstetrical	4	5	3	6	2	11		0	0		0	0	
Therapy planning	63	80	42	84	11	58		3	100		6	86	
Maternal deterioration	7	9	3	6	3	16		0	0		1	14	
Other	1	1	0	0	1	5		0	0		0	0	
Reason elective CS (n = 70)			N = 51		N = 11		.226	N = 2		.568	N = 6		.599
Maternal obstetrical	23	33	18	35	2	18		0	0		3	50	
Fetal obstetrical	6	9	4	8	2	18		0	0		0	0	
Maternal clinical/oncological	41	59	29	57	7	64		2	100		3	50	
Mode delivery							.101			.176			.481
Vaginal	112	56	64	51	28	65		7	70		13	59	
Cesarean section	82	41	59	47	13	30		2	20		8	36	
Not reported	7	3	3	2	2	5		1	10		1	5	
Abnormal Dopplers							.001			na			na
No	133	96	85	100	29	85		5	100		14	100	
Yes	5	4	0	0	5	15		0	0		0	0	
Not reported	63		41		9			5			8		
Oligohydramnion							.037			1			1.000
No	195	97	124	98	39	91		10	100		22	100	
Yes	6[b]	3	2	2	4	9		0	0		0	0	

GA: gestational age; na: not applicable.
The characteristics of the fetal growth restricted (FGR) group, "low risk SGA" group and "Fetal growth disturbance" group are compared to the group with normal fetal growth (no impact growth).
[a]Including four women with breast cancer that only received taxanes during pregnancy.
[b]Treatment with (1) cisplatin (6×), (2) doxorubicin-cyclophosphamide (4×) and paclitaxel (4×), (3) epirubicin-cyclophosphamide (4×), (4) doxorubicin-cyclophosphamide (2×), (5) BEACOPP (6×), and (6) EPOCH (4×).

sonographic findings. Placental pathology revealed villous fibrosis and a large hematoma.

There were no significant differences in oncological characteristics between *FGR* and *non-FGR* cases. In the FGR group, the maternal weight gain was lower ($p = .033$) compared and more women started chemotherapy prior to 20 weeks of gestation ($p = .036$). In 144 pregnancies, Doppler studies were reported. All cases with abnormal Doppler measurements were allocated to the FGR group ($n = 5$).

Median gestational age at delivery was 37 weeks (range 29–40). Most deliveries were planned for obstetric or medical reasons (149 of 201, 74%). Only 10/201 (4.9%) women had an planned delivery because of fetal reasons (e.g. FGR). Preterm delivery was reported in 105 (52%) women, including 19 women with spontaneous preterm labor (9%).

Effects of chemotherapy on birth weight

Univariable regression analysis showed that early *gestational age at initiation of chemotherapy* (1.09; 95%CI 0.38; 1.81, $p < .01$) and longer *duration* thereof (−0.79; 95%CI −1.61; 0.02, $p = .06$), low *maternal BMI* (1.30;
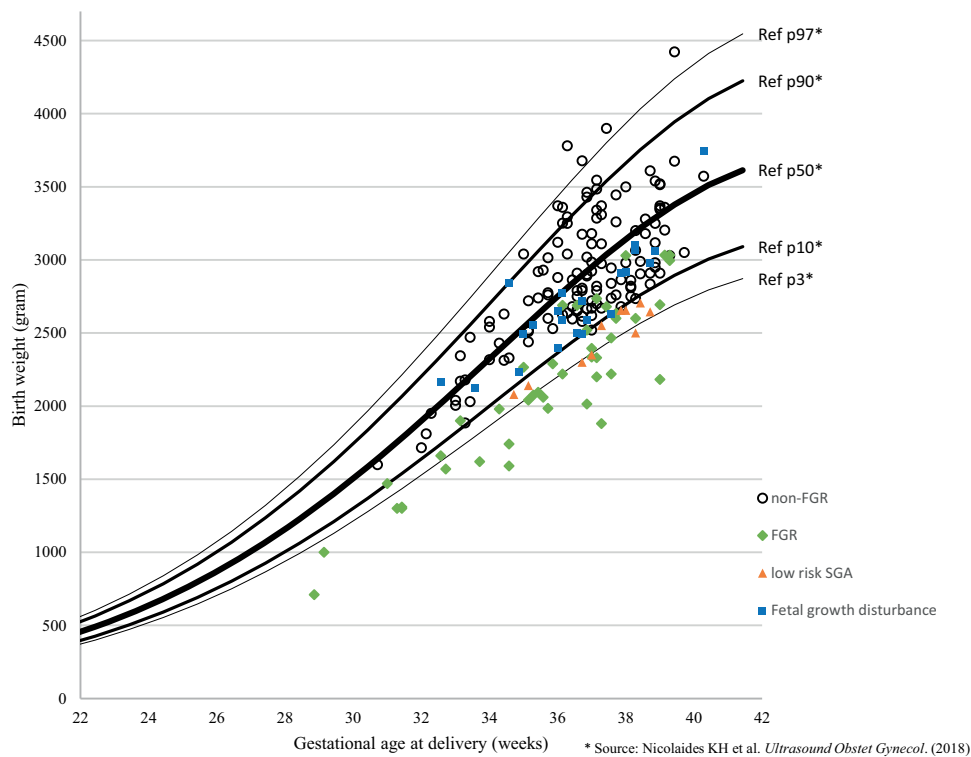
Figure 1. Scatter plot of birthweight according to gestational age at delivery, plotted on the reference chart by Nicolaides et al. [16] (*n* = 201).

95%CI 0.39; 2.22, *p* < .01), *systemic disease* (−10.23; 95%CI −22.98; 2.52, *p* = .12), low *gestational weight gain* (0.17; 95%CI −0.01; 0.34, *p* = .07), *hypertensive disorders* (−31.14; 95%CI −65.55; 2.26, *p* = .07), *parity (nulliparity)* (8.00; 95%CI −1.20; 16.20, *p* = .06), and *female neonatal sex* (−7.57; 95%CI −0.67; 15.81, *p* = .07) were associated with lower birth weight percentile (Supplementary Table 1).

In this heterogeneous series, we identified *diabetes*, *maternal age*, *ethnicity*, and *cancer type* as clinically relevant confounders for fetal growth [21]. As most women (*n* = 158, 79%) received anthracyclines, and previous research revealed a higher risk for SGA with taxanes and platinum, we additionally corrected for the receipt of *taxanes* and/or *platinum* in multivariable analysis [5]. In multivariable analysis, the duration of antenatal chemotherapy (in weeks) remained negatively associated with birth weight percentile (−1.06; 95%CI −2.01; −0.04; *p* = .04), and gestational age at initiation of chemotherapy (in weeks) showed a positive correlation (1.10; 95%CI 0.26; 1.95; *p* = .01) (Supplementary Table 1).

Effect of chemotherapy on fetal growth

The LME models revealed that a longer duration of chemotherapy (in weeks) was related to lower EFW, AC, HC, and FL percentiles (−0.253; 95%CI −0.315;

−0.191, *p* < .001; −0.234; 95%CI −0.280; −0.189, *p* < .001; −0.200; 95%CI −0.034 to 0.117, *p* < .001; and 0.035; 95%CI −0.039; 0.108, *p* < .001, respectively) (Supplementary Table 2 and Supplementary Figure 3). In these models, the duration of antenatal chemotherapy appeared to have a greater influence on fetal growth compared to gestational age at chemotherapy initiation. The later chemotherapy was initiated, the higher the negative impact on EFW, AC, and HC (with a constant chemotherapy duration).

Discussion

In this cohort study of pregnant cancer patients treated with chemotherapy, of whom 66% had breast cancer, 79% received anthracyclines and 88% delivered after 34 weeks of gestation, we found that over one third of the pregnancies was complicated by impaired fetal growth, including 21% FGR. Disease-related factors that were associated with FGR were systemic disease and low gestational weight gain, both associated with general maternal health and nutrition. The current data show that there is a strong correlation between low birth weight and a longer duration of chemotherapy exposure on the one hand and, likewise, low birth weight and an earlier gestational age at initiation of chemotherapy on the other. Nevertheless, when controlling for chemotherapy

duration, it appeared that chemotherapy initiation later in pregnancy resulted in a stronger impairment of fetal growth.

The literature about chemotherapy related FGR describes conflicting results; the largest cohorts, revealed an increased risk of SGA, where others, including population-based studies, do not confirm this [5,23–27]. To date, research in this field focused on birth weight only, potentially misjudging or underestimating the problem of FGR. Here, we confirm the high incidence of FGR in pregnant women receiving chemotherapy. However, not all fetuses are growth impaired and the majority do show a reassuring growth. The multifactorial etiology of FGR apart from exposure to cytotoxic drugs, including maternal nutritional status and disease severity, psychological stress, the presence of hypertensive disorders or diabetes, is reflected in these data. Factors interfering with fetal growth will have most impact when occurring in the third trimester of pregnancy, as EFW growth velocity increases across gestation, with a peak acceleration in the third trimester of pregnancy (35 weeks of gestational age) [28].

All maternal, placental, and fetal factors play a role in the etiology underlying FGR [10].

In (pregnant) cancer patients poor nutrition and general health, primary by cancer and secondary by the adverse effects of cancer treatment and cancer-related stress, are major determinants [29,30]. In this series, only 21% (32 of 151 data available) patients met IOM standards for maternal weight gain [31]. A cancer diagnosis results in both physical as emotional stress [32,33]. There is increasing evidence that prenatal stress disrupts maternal and fetal endocrine (cortisol-related pathways involving the hypothalamic–pituitary–adrenal (HPA) axis), nervous and immune (increased cytokine release) systems, hereby affecting pregnancy outcomes, including preterm birth and FGR [34]. Prenatal stress is reported to directly interfere with the insulin growth factor (IGF) system, involved in the regulation of fetal, placental, and neonatal growth [35].

Placental changes following chemotherapy exposure include histologic disturbances related to impaired maternal–fetal nutrient supply as well as placental oxidative damage and apoptosis affecting placental growth and function [36–38]. A case control study, evaluating chemotherapy-exposed placentas from women with cancer and placentas from healthy controls, confirmed increased oxidative (DNA) damage in chemotherapy-exposed placentas, with an increasing effect with longer chemotherapy exposure [38]. Also, chemotherapy might induce DNA damage and epigenetic changes in the unborn child, affecting growth and health on the long-term [39].

Follow-up studies of children prenatally exposed to chemotherapy reveal that SGA children will eventually catch up growth [40,41]. This implicates that adverse fetal effects are rather transient, without affecting the postnatal growth potential. It remains unclear whether chemotherapy itself or the disease-related stress and inflammation is the dominant factor in impaired fetal growth; most likely it is a combination thereof.

With the relative low molecular weight and lower plasma protein binding, platinum derivatives will cross the placenta more easily compared to anthracyclines [42–44]. Although measured fetal plasma concentrations are low, the strong tissue-binding capacity of taxanes results in measurable concentrations in fetal tissues [42,45,46]. Based on earlier reports, we hypothesized that low birth weight percentiles would mainly be seen in patients exposed to taxanes and platinum, but we could not confirm this [5]. However, this cohort is relatively small compared to previous series and the heterogeneous cancer treatments and multidrug use complicate the detection of specific drug interactions [5].

This cohort study reveals a negative impact of the duration of chemotherapy on fetal growth; however, the actual cause of impaired fetal growth is most likely explained by the (longer duration of) exposure to multiple factors including cytotoxic agents, co-medications, maternal physical and psychological stress and malnutrition. In clinical practice, oncological management should adhere to standard protocols, while continuously balancing maternal and fetal risks. In order to preserve maternal prognosis antenatal treatment should not be postponed. Fetal surveillance includes serial growth scans and patients with an oncological diagnosis early in pregnancy and a presumed long antenatal treatment are at highest risk of impaired fetal growth.

This is an observational study to assess FGR in a selected group of pregnant women receiving chemotherapy, based on predefined criteria. However, management of FGR in cancer patients is case-specific and should not be extrapolated from this retrospective series. The variance in numbers of available ultrasound and performed Doppler measurements between patients is a consequence of the difference in local policies in obstetric follow-up of pregnant patients receiving chemotherapy and the lack of an international consensus. The lack of a detailed ultrasound reporting system in some hospitals, explains why relatively few cases with available ultrasounds could be selected from

the large INCIP registry. Also, this cohort is subject to selection bias as fetal ultrasounds may have been performed because of an assumed high risk of fetal growth abnormalities. The majority of the participating hospitals counsel pregnant cancer patients in a routine way for INCIP registration. In terms of distribution of cancer types, duration of antenatal chemotherapy and mean birth weight this series appears representative for the INCIP database. The results of this series should be interpreted with caution because multiple confounders for fetal growth in this high-risk population complicate data interpretation. Due to the retrospective study design, large amount of data were missing (e.g. on BMI, gestational weight gain, smoking/substance use during pregnancy). Also, we could not further explore placental histopathological findings. Future research on antenatal chemotherapy should not only focus on clinical data, but also on placental histopathology and FGR-related biomarkers in order to unravel the exact mechanism of chemotherapy-induced FGR. Larger prospective, more homogeneous cohorts are needed to further focus on effects of specific chemotherapy regimens and investigate a dose–effect of chemotherapy on fetal growth and birth weight, as suggested by these data. In this cohort study, racial disparities cannot be discussed properly as non-Caucasian women are underrepresented. The INCIP initiative strives to continue to collect data in a multicenter, international setting and collaborate with more hospitals around the globe to adjust for these disparities [47].

This study reveals that prenatal exposure to chemotherapy is a risk factor for FGR. Pregnant cancer patients should be followed in a high-risk obstetric unit with a close surveillance of the fetal growth, especially in the third trimester of pregnancy.

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