# Impact of chemotherapy during pregnancy on fetal growth

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**Conflict of interest statement**

The authors report no conflict of interest.

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**Keywords**

Chemotherapy, cancer, pregnancy, fetal growth restriction, small for gestational age

## 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 < $10^{th}$ 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, diabetes) and individual cytotoxic agents (anthracycline, taxanes, 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 $10^{th}$ percentile), but an estimated growth above the $10^{th}$ 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=0.04) and poor maternal gestational weight gain (median percentile 15 (range 0-97) vs 8 (0-84), p=0.03) 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 and maternal BMI as confounders. Multivariable regression revealed that each additional week of chemotherapy was associated with lower birth weight percentiles (-1.06; 95%CI -2.06; -0.06; p=0.04), and that later initiation of chemotherapy was associated with an increase in birth weight percentile (1.12 per week; 95%CI 0.27; 1.97; p=0.01). Each additional week of chemotherapy was associated with lower EFW and abdominal circumference (AC) percentiles (-1.77; 95%CI -2.21; -1.34, p<0.001; -1.64 95%CI -1.96;-1.32, p<0.001, respectively).

**Conclusion(s)**

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.

**Keywords**

Chemotherapy, cancer, pregnancy, fetal growth restriction, small for gestational age

## 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 10$^{th}$ 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. Secondly, SGA does not properly represent FGR, as mentioned above. Thirdly, 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 young 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 included TNM or FIGO stage IV disease and locally advanced disease with organ dysfunction. 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.[12] 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 et al.[13] The EFW from each examination was derived from Hadlock's formula, based on HC, AC and FL.[14] EFW and birth weight by gestational age were expressed as crude percentiles, reported by the Fetal Medicine Foundation.[15] 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 10$^{th}$ customized percentile, they were defined as SGA. Customized percentiles were calculated for birth weight, corrected for gestational age, ethnicity, neonatal gender, maternal pre-pregnancy BMI and parity.[16] Placental weight was corrected for gestational age at delivery.[17] Abnormal Doppler measurements were defined as Pulsality index (PI) of the umbilical artery >95$^{th}$ percentile according to the references by the Fetal Medicine Foundation.[18]. The cerebroplacental ratio is defined as the ratio of the middle cerebral artery PI to the umbilical artery PI and assumed abnormal when <5$^{th}$ percentile.[18]

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 3$^{rd}$ percentile or ultrasonographic features defined by a Delphi consensus in 2016 (*the FGR group*).[6,19] FGR before 32 weeks (early FGR) was defined as an AC or EFW percentile below the 3$^{rd}$ percentile or absence of end-diastolic umbilical flow or AC/EFW below the 10$^{th}$ centile in combination with abnormal Dopplers of the uterine artery or the umbilical artery (above the 95$^{th}$ percentile). FGR after 32 weeks (late FGR) was defined as AC/EFW below the 3$^{rd}$ percentile or at least two out of three of the

following; EFW below the 10th percentile, AC/EFW crossing ≥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.[13] Because of the inherent poor predictive value of ultrasound, a second and a third group 'at risk' were defined.

2) 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*).

3) 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 ≥50 centiles during the course of pregnancy or EFW/AC percentile below the 10th percentile (*the 'fetal growth disturbance' group*).

4) 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 exact test in case of frequencies lower than five, and Mann Whitney 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 a significant association with fetal growth in the univariable analysis ($p<0.2$) or if identified as clinically relevant. In addition, ethnicity, parity and neonatal gender were added to the multivariable models. A linear mixed-effects model (LME) for repeated measures was

used to identify the possible influence of initiation and total duration of chemotherapy on fetal growth, assessed by biometric measurements (EFW, AC, HC and FL).[20] All tests were two-sided, and a p=5% threshold for statistical significance was assumed for all tests. Analyses were performed using SAS software (version 9.4 of the SAS System for Windows) and R (version 3.6.0).

## Results

### *Study population*

Out of 1008 pregnancies with antenatal chemotherapy registered in the INCIP database, 201 women were eligible (Supplementary Figure 1). Between all INCIP cases, including those with <2 prenatal scans, and our study group no significant difference was observed with regard to birth weight percentile (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 percentiles. 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 a 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%). Early FGR (<32 weeks of gestation) occurred in 19/43 growth restricted fetuses (44%) and 7/43 growth restricted fetuses (16%) 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 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=0.033) compared and more women started chemotherapy prior to 20 weeks of gestation (p=0.036). 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 (eg. FGR). Preterm delivery was reported in 105 (65%) 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 and longer duration thereof, systemic disease, low gestational weight gain, hypertensive disorders and low maternal BMI were associated with lower birth weight percentile (Supplementary Table 1).

As most women in this series (n=158, 79%) received anthracyclines, and previous research revealed a higher risk for SGA with taxanes and platinum, we corrected for the receipt of taxanes and/or platinum in multivariable analysis.[5] In addition, diabetes, maternal age at diagnosis, and cancer type were identified as important clinically relevant confounders for fetal growth. As the effect of gestational age at initiation of chemotherapy and duration of chemotherapy exposure were highly correlated, both variables could not be used in one model. In multivariable analysis, the duration of antenatal chemotherapy (in weeks) was negatively associated with birth weight percentile (-1.06; 95%CI -2.06; -0.06; p=0.04), and gestational age

at initiation of chemotherapy (in weeks) showed a positive correlation (1.12; 95%CI 0.27; 1.97; p=0.01) (Supplementary table 1).

***Effect of chemotherapy on fetal growth***

The linear mixed effects 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<0.001; -0.234 95%CI -0.280;-0.189, p<0.001; -0.200 95%CI -0.034-0.117, p<0.001; and 0.035 95%CI -0.039;0.108, p<0.001 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.[5,21-25] 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).[26]

Both 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. In this series, only 21% (32 of 151 data available) patients met IOM standards for maternal weight gain.[27] 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.[28] Prenatal stress is reported to directly interfere with the insulin growth factor (IGF) system, involved in the regulation of fetal, placental and neonatal growth.[29]

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.[30-32] 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.[32] Also, chemotherapy might induce DNA damage and epigenetic changes in the unborn child, affecting growth and health on the long-term.[33]

Follow-up studies of children prenatally exposed to chemotherapy reveal that SGA children will eventually catch up growth.[34,35] 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-derivates will cross the placenta more easily compared to anthracyclines.[36-38] Although measured fetal plasma concentrations are low, the strong tissue-binding capacity of taxanes results in measurable concentrations in fetal tissues.[36,39,40] 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. Because of 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. Collection of data is challenging and should be organized in a multicenter setting.

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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## Disclosure of interest

The authors report no conflict of interest.

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## Tables

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

| | Total | Non-FGR | 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) | 33 (24-46; 8) | 0.598 | 33 (24-43; 10) | 0.254 | 33 (19-41; 7) | 0.280 |
| **Maternal BMI at booking (kg/m2)** | 24 (16-42; 7) | 25 (18-42; 7) | 22 (16-38; 5.9) | 0.021 | 24 (19-28; 4) | 0.263 | 25 (19-33; 3) | 0.927 |
| **Gestational weight gain (kg)** | 7 (-9–25; 6) | 7 (-7-25; 7) | 5.9 (-9–18; 5) | 0.085 | 8 (2-22; 4) | 0.820 | 7 (1–16; 6) | 0.473 |
| **Maternal weight gain (percentile) (Santos)*** | 13 (0-97; 32) | 15 (0-97; 37) | 8 (0-84; 28) | 0.033 | 7 (0-96; 21) | 0.197 | 10 (1-74; 27) | 0.473 |
| **GA chemo initiation (weeks)** | 22 (12-34; 9) | 23 (12-34; 8) | 20 (13-32; 10) | 0.042 | 17 (16-22; 5) | 0.004 | 22 (12-33; 10) | 0.325 |
| **Duration of chemo during pregnancy (weeks)** | 12.3 (2-26; 7) | 2 (2-26; 7) | 12 (3-22; 8) | 0.560 | 16 (7-20; 5) | 0.026 | 14 (3-24; 9) | 0.284 |
| **Number of courses of chemotherapy** | 5 (1-16; 3) | 4 (1-16; 3) | 4 (1-16; 4) | 0.715 | 7 (5-12; 7) | 0.002 | 6 (1-16; 6) | 0.134 |
| **GA delivery (weeks)** | 37 (29-40; 3) | 37 (31-40; 2) | 36 (29-39; 3) | 0.046 | 38 (35-39; 2) | 0.393 | 37 (33-40; 3) | 0.499 |
| **Crude birthweight percentile** | 30 (1-100; 46) | 47 (10-100; 52) | 3 (1-39; 14) | <0.001 | 7 (3-9; 5) | <0.001 | 28 (10-90; 23) | 0.002 |
| **Customized birth weight percentile**** | 32 (0-99; 47) | 46 (4-100; 44) | 4 (0-41; 16) | <0.001 | 8 (3-17; 9) | <0.001 | 25 (11-91; 32) | 0.032 |
| **Placental weight (grams)***** | 394 (136-750; 158) | 435 (243-750; 166) | 308 (136-574; 113) | <0.001 | 294 (199-421; 157) | 0.008 | 391 (332-750; 103) | 0.546 |
| **Placenta percentile (Thompson)** | 4 (2-85;13) | 8 (2-80; 27) | 2 (2-31; 3.3) | 0.004 | 2 (2-3; 0) | 0.214 | 5 (2-85; 11.3) | 0.498 |

For all characteristics the median (range; interquartile range) are given

Abbreviations: BMI: Body Mass Index; cm: centimeter; kg: kilogram; GA: gestational age

*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.

** according to the reference chart reported by Gardosi et al.

*** 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. 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)**

| | Total | | Non-FGR | | FGR | | p-value | Low risk SGA | | p-value | Fetal growth disturbance | | p-value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Total N** | 201 | | 126 | | 43 | | | 10 | | | 22 | | |
| | **N.** | **%** | **N.** | **%** | **N.** | **%** | | **N.** | **%** | | **N.** | **%** | |
| **Cancer type** | | | | | | | 0.847 | | | 0.287 | | | 0.265 |
| 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** | | | | | | | 0.503 | | | 0.894 | | | 0.027 |
| 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** | | | | | | | 0.623 | | | 1.000 | | | 0.746 |
| 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** | | | | | | | 0.036 | | | 0.011 | | | 0.320 |
| <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** | | | | | | | 0.222 | | | 0.005 | | | 0.198 |
| <16 | 25 | 12 | 12 | 10 | 8 | 19 | | 0 | 0 | | 5 | 23 | |
| 16-19.9 | 43 | 21 | 20 | 16 | 12 | 28 | | 7 | 70 | | 4 | 18 | |
| 20-23.924-27, | 55 | 27 | 38 | 30 | 10 | 23 | | 3 | 30 | | 4 | 18 | |
| 28-31.9 | 37 | 18 | 27 | 21 | 6 | 14 | | 0 | 0 | | 4 | 18 | |
| >32 | 30 | 15 | 23 | 18 | 5 | 11 | | 0 | 0 | | 2 | 9 | |
| | 11 | 5 | 6 | 5 | 2 | 5 | | 0 | 0 | | 3 | 14 | |
| **Maternal BMI** | | | | | | | 0.030 | | | 0.321 | | | 0.686 |
| <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** | | | | | | | 0.278 | | | 0.091 | | | 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** | | | | | | | 1.000 | | | 0.623 | | | 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** | | | | | | | 0.160 | | | 1.000 | | | 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** | | | | | | | 0.094 | | | 0.604 | | | 0.241 |
| Local | 178 | 89 | 115 | 91 | 35 | 81 | | 10 | 100 | | 18 | 82 | |
| Systemic | 23 | 11 | 11 | 9 | 8 | 19 | | 0 | 0 | | 4 | 18 | |
| **Diabetes** | | | | | | | 0.204 | | | 1.000 | | | 0.592 |
| No | 195 | 97 | 120 | 95 | 43 | 100 | | 10 | 100 | | 22 | 100 | |
| Yes | 6 | 3 | 6 | 5 | 0 | 0 | | 0 | 0 | | 0 | 0 | |
| **Treatment** | | | | | | | 0.103 | | | 0.239 | | | 0.563 |
| Anthracyclines | 121 | 60 | 80 | 65 | 21 | 49 | | 5 | 50 | | 15 | 68 | |
| (Anthracyclines +) Taxanes* | 45 | 22 | 22 | 17 | 14 | 32 | | 4 | 40 | | 5 | 23 | |
| Platinum-based | 35 | 17 | 24 | 19 | 8 | 19 | | 1 | 10 | | 2 | 9 | |
| **Anthracyclines** | | | | | | | 0.525 | | | 0.227 | | | 0.252 |
| No | 43 | 21 | 26 | 21 | 11 | 26 | | 4 | 40 | | 2 | 9 | |
| Yes | 158 | 79 | 100 | 79 | 32 | 74 | | 6 | 60 | | 22 | 91 | |
| **Taxanes** | | | | | | | 0.812 | | | 1.000 | | | 0.148 |
| No | 141 | 70 | 105 | 83 | 37 | 86 | | 9 | 90 | | 17 | 77 | |
| Yes | 60 | 30 | 21 | 17 | 6 | 14 | | 1 | 10 | | 5 | 23 | |
| **Platina** | | | | | | | 0.713 | | | 1.000 | | | 0.766 |
| No | 163 | 81 | 103 | 82 | 59 | 79 | | 8 | 80 | | 19 | 86 | |
| Yes | 38 | 19 | 23 | 18 | 16 | 21 | | 2 | 20 | | 3 | 14 | |
| **NICU admission** | | | | | | | 0.764 | | | 1.000 | | | 0.695 |
| No | 129 | 64 | 115 | 91 | 38 | 88 | | 9 | 90 | | 21 | 95 | |
| Yes | 53 | 26 | 11 | 9 | 5 | 12 | | 1 | 10 | | 1 | 5 | |
| **GA delivery** | | | | | | | 0.003 | | | 0.510 | | | 0.554 |
| <32 weeks | 7 | 3 | 1 | 1 | 6 | 14 | | 0 | 0 | | 0 | 0 | |
| 32-34 weeks | 17 | 8 | 11 | 9 | 4 | 9 | | 0 | 0 | | 2 | 9 | |
| 34-37 weeks | 81 | 40 | 51 | 40 | 15 | 35 | | 3 | 30 | | 12 | 55 | |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| >37 weeks | 93 | 48 | 63 | 50 | 18 | 42 | | 7 | 70 | | 8 | 36 | |
| **Onset of labor** | | | | | | | 0.194 | | | 0.123 | | | 0.118 |
| 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 | |
| Missing | 7 | 3 | 3 | 2 | 2 | 5 | | 1 | 10 | | 1 | 5 | |
| **Spontaneous preterm labor** | | | | | | | | | | 1.000 | | | 0.037 |
| No | 182 | 91 | 117 | 93 | 39 | 91 | 0.813 | 9 | 90 | | 17 | 77 | |
| Yes | 19 | 9 | 9 | 7 | 4 | 9 | | 1 | 10 | | 5 | 23 | |
| **Reason of IOL (n=79)** | | | N=50 | | N=19 | | 0.229 | N=3 | | 1.000 | N=7 | | 0.936 |
| 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 | | 0.226 | N=2 | | 0.568 | N=6 | | 0.599 |
| 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** | | | | | | | 0.101 | | | 0.176 | | | 0.481 |
| 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** | | | | | | | 0.001 | | | 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** | | | | | | | 0.037 | | | 1.000 | | | 1.000 |
| No | 195 | 97 | 124 | 98 | 39 | 91 | | 10 | 100 | | 22 | 100 | |
| Yes | 6** | 3 | 2 | 2 | 4 | 9 | | 0 | 0 | | 0 | 0 | |

Abbreviations: GA: gestational age; na: not applicable

* Including four women with breast cancer that only received taxanes during pregnancy

*Treatment with 1. Cisplatin (6x), 2. Doxorubicin-Cyclophosphamide (4x) and paclitaxel (4x), 3. Epirubicin-cyclophosphamide (4x), 4. Doxorubicin-cyclophosphamide (2x), 5. BEACOPP (6x), 6. EPOCH (4x)

478 **Figures**

479 **Figure 1: Scatter plot of birthweight according to gestational age at delivery, plotted on the reference chart by Nicolaides et al., 2018 (n=201).**

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