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Chemotherapy is avoided during the first trimester of pregnancy, when is the safest time to start treatment during the second or third trimester?

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ABSTRACT

Background

Cancer occurs in approximately 1:1000 pregnancies. When chemotherapy cannot be delayed until postpartum, beginning chemotherapy is based on presumed safety after organogenesis is completed during the first trimester. The safest gestational age to start chemotherapy after the first trimester is unknown.

Patients and Methods

In an observational cohort of pregnant women diagnosed and treated for cancer at multiple centers, pregnancy outcomes for the mother, and clinical outcomes for the neonate were analyzed according to the gestational age in weeks of pregnancy at first chemotherapy cycle. Outcomes including birth weight, fetal growth restriction, congenital malformations, and perinatal complications for mother and infant were analyzed according to gestational age of chemotherapy initiation. Neonatal growth, general health and developmental assessment were provided annually by each child's pediatrician. For each outcome, cut-point of gestational age at first chemotherapy after 12 weeks was determined with odds ratios (OR).

Results

Data from 225 women (231 fetuses) were analyzed. Initiating chemotherapy before 15 weeks GA significantly increased risk for intrauterine growth restriction (OR=3.0), before 16.6weeks GA increased risk for congenital anomalies (OR=3.9), and before 18 weeks GA increased risk for spontaneous preterm birth (OR=2.3). Maternal and neonatal complications during pregnancy or follow up were not statistically different based on GA when chemotherapy began.

Conclusions

During the second trimester, the ideal time to start chemotherapy should consider maternal benefit versus neonatal risk. With a history of spontaneous preterm birth in a prior pregnancy, delaying chemotherapy until 18 weeks may decrease recurrent preterm birth, if not detrimental to the mother. The risk for fetal growth restriction increased with chemotherapy initiation before 15 weeks, and for congenital malformations before 17 weeks.

KEYWORDS: Chemotherapy, Cancer, Pregnancy, Trimester

INTRODUCTION

Cancer is uncommonly diagnosed during pregnancy, but the incidence is increasing due to delayed childbearing. The most common cancers affecting reproductive age women are breast, cervical, thyroid, melanoma and Hodgkin's lymphoma [1]. Termination of pregnancy has not been shown to improve patient survival [2-5]. Except for indolent chronic lymphomas, early-stage Hodgkin's Lymphoma, or patients diagnosed late in the third trimester, delaying chemotherapy until after delivery may compromise maternal survival. Case reports or retrospective series limited to infant condition at birth comprise the majority of the current literature on chemotherapy use in pregnancy [6-13]. This spurred the creation of the Cancer and Pregnancy Registry Cohort Study to prospectively follow pregnant women diagnosed with cancer at multiple centers and note the outcomes of the children long term. This cohort includes women treated internationally. It has become the de facto standard that chemotherapy is avoided during the first trimester, when fetal organogenesis occurs and anomalies have been reported with first trimester exposures [6]. No previous study has compared the neonatal consequences, if any, between second and third trimester exposure. The ideal time to begin chemotherapy after organogenesis is in fact not known. In this study, only looking at chemotherapy exposures after 12 weeks gestational age (GA), we evaluate fetal and maternal outcomes of initiating chemotherapy during the second versus third trimester of pregnancy. Our primary objective is to determine how the gestational age at which chemotherapy is started may affect neonatal or pregnancy complications.

MATERIAL AND METHODS

Design, Setting, and Participants, this is an observational cohort study of pregnant women enrolled in the Cancer and Pregnancy Registry study (on ClinicalTrials.GovNCT02749474). Inclusion criteria: the diagnosis of cancer during pregnancy, i.e. for any woman between the date of their last menstrual period and the end of pregnancy either by miscarriage or delivery. Women who were diagnosed postpartum were excluded. All registered patients diagnosed with primary cancer between January 1, 1994, and January 31, 2016, were eligible for inclusion, independent of outcome of the pregnancy, cancer type or treatment. Creation of this observational cohort was approved by the Institutional Review Board of Cooper Medical School at Rowan University, and written informed consent was obtained from patients before prospective inclusion at the time of diagnosis in pregnancy. Patient country of treatment does not affect enrollment. Enrollment is ongoing. Pregnancy and neonatal outcomes were analyzed according to GA at first chemotherapy treatment. Outcomes include GA at birth, birthweight and incidence of intrauterine growth restriction (IUGR) defined as birthweight percentile <10%, incidence of spontaneous preterm birth <35weeks, congenital anomalies, neonatal neutropenia based on complete blood count and differential collected on first day of life, perinatal complications, and long-term medical and behavioral diagnoses for the infant. . For birthweight percentile, the customized GROW centile calculator (version 8.0.1 (2018) from www.gestation.net was used to calculate a birth weight percentile [14]. Maternal complications include gestational diabetes, placenta previa or abruption, postpartum hemorrhage, and depression during pregnancy or postpartum. Spontaneous preterm delivery is counted after excluding elective iatrogenic preterm births. Neonatal complications include respiratory distress, tachypnea, apnea or anemia of prematurity, hyperbilirubinemia, sepsis or rashes. Complications related to birth defects, such as a urinary tract infection due to vesicoureteral reflux from urologic anomalies are not additionally counted in this category. Height and weight percentiles, general developmental assessment, and treatment for medical conditions are assessed by each child's pediatrician annually. To monitor the development of children exposed to chemotherapy in utero standardized motor, language, and cognitive assessments were performed using the Bayley III, Wechsler Individual Achievement Test-Third Edition WIAT or Wechsler Preschool and Primary Scale of Intelligence (WHIPPSI) at appropriate ages. Parents were asked to assess childhood clinical behavioral using the Complete Behavioral Checklist (CBCL). Major birth defects were defined according to the Metropolitan Atlanta Congenital Defects Program code modifications developed by the Division of Birth Defects and Developmental Disabilities, U.S. Department of Health and Human Services. Statistical comparisons were made for primary outcomes based on GA when treatment began. For each outcome, GA at first chemotherapy treatment was analyzed for a significant cut-point using recursive partitioning. Odds ratios with 95% confidence intervals were calculated using logistic regression. Gestational age at birth was used to adjust effects on outcomes as appropriate. All analyses were done using SAS v9•4 (SAS Institute, Cary, NC).

RESULTS

Descriptive demographics are described here, followed by tables for pregnancy and neonatal outcomes. An international cohort of 225 women with cancer and 231 fetuses (including 6 sets of twins) who were treated with chemotherapy after 12 weeks of pregnancy were identified from the Cancer and Pregnancy Registry cohort. Cancer types included breast (159); Hodgkin's disease (24); non-Hodgkin's lymphoma (12); ovarian (11); colorectal (7); cervical (5); acute leukemia (2); and

choriocarcinoma (1), sarcoma (1), chronic leukemia and bladder (1), bone (1), and pancreatic (1).The most common chemotherapy regimens in pregnancy were doxorubicin/cyclophosphamide;5-fluouracil/doxorubicin/cyclophosphamide: and doxorubicin/bleomycin/vinblastine/dacarbazine. Mean fetal GA at cancer diagnosis for the entire cohort regardless of GA at treatment initiation was 20•7 (SD 5.4) weeks, and the mean number of chemotherapy cycles was 4•3 (SD 2.1). Mean GA at delivery was 36•4 (SD 2•6) weeks; mean birth weight was 2588 (SD 636) grams. Mean GA at first chemotherapy treatment was 21•2 weeks (SD 5•5). Mean stage at diagnosis was II. In Table 1, outcomes are compared by gestational age at which chemotherapy was started for the following outcomes: GA at delivery, mean neonatal birthweight, incidence of spontaneous preterm birth, and intrauterine growth restriction (IUGR).

Mean Gestational Age at Delivery, Mean Birth Weight (in weeks) Gestational age at delivery				
Trimester of Diagnosis (weeks)	**12-24**	**≥ 25**	**Total**	***p***
Mean gestational age at Delivery (weeks)	36.5±2.66	36.6±2.26	36.4±2.6	0.95
N Pregnancies	166	59	225	
Mean birth weight (grams)	2552±645	2789±596	2588±636	**.03**
N Infants	*172	59	231	
***twins Spontaneous Preterm Birth**				
	12-24	**≥ 25**	**Total**	***p***
Spontaneous Preterm birth <37weeks	32	9	41	
N Pregnancies	166	59	225	
Preterm birth<37weeks (%)	19.2	15.2	18.2	0.49
Spontaneous Preterm birth <35weeks	*18*	*5*	*23*	
N Pregnancies	*146*	*50*	*225-29iatrogenic preterm birth <35w=196*	
Preterm birth <35 weeks (%)	*12.3%*	*10%*	*11.7%*	*0.66*
Incidence Intrauterine Growth Restriction - IUGR=Birth weight <10% for gestational age at birth				
	12-24	***≥ 25***	***Total***	***p***
IUGR (Birth percentile<10%)	*42*	*11*	*53*	
N Infants	139	47	186	
IUGR (%)	30%	23.4%	28.5%	0.37

Table1: *Mean Gestational Age at Delivery and Mean Birth Weight, Non-Iatrogenic Premature Birth Prior to 37 Gestational Weeks, and Intrauterine Growth Restriction according to Gestational Age at First Cycle of Chemotherapy*.

There was a significantly lower mean birthweight in the group starting chemotherapy between 12-24 weeks compared to the group beginning treatment after 25 weeks, 2552 +645g vs 2789 +596g, p=0.03. There was no significant difference in spontaneous preterm deliveries prior to 37weeks when chemotherapy was started between 12-24 weeks compared to after 25.0 weeks, 19.2% versus 15.2 %, p=0.49. In 82 cases, an elective preterm birth iatrogenically occurred in order to resume cancer therapy without waiting for spontaneous labor. The majority of these occurred between 35 and 37weeks. After excluding 29 iatrogenic (elective) preterm deliveries (< 35 weeks), the incidence of early spontaneous preterm birth was 11.7%, occurring in 23/196 pregnancies. There remained no significant difference in the incidence of spontaneous preterm birth between the group starting chemotherapy 12-24 weeks, and those starting after 25 weeks gestational age, p=.0.66 For 45 deliveries, despite having the gestational age, birthweight and gender missing demographics for the mother would not allow a calculation of a birthweight percentile. For the remaining 186 infants for which a birthweight percentile could be calculated using gestation.net, the overall incidence of IUGR (birth percentile <10%) was 53/186 (28.5%). There was no significant difference in the incidence of IUGR between starting chemotherapy 12-24 weeks versus after 25 weeks, 30% vs. 23.4%, p=0.28.

Seven major birth defects (3•1%) were reported for the cohort at birth. The purpose of longitudinal follow up for this cohort is to detect any anomalies diagnosed up until 5 years of age. In fact, 12 additional children were diagnosed with a birth defect between 1 and 22 months of age. In Table 2, the incidence of congenital anomalies diagnosed in early childhood is compared between the 2 treatment groups.

Incidence of Major Birth Defects				
	12-24	**≥ 25**	**Total**	***p***
Birth Defect *N*	18	1	19	
Birth Defect (%)	10.5%	1.7%	8.2%	0.05
N Infants	172	59	231	
Incidence of Neonatal Neutropenia at Birth				
	12-14*	**≥ 25**	**Total**	***p***
Neutropenia *N*	4	0	4	
Neutropenia (%)	23.3%	0%	1.7%	0.57
Preterm birth?	Yes, 34.9- 36.6wks			
Days Between Chemotherapy & Delivery	21-98			
N Infants	172	59	231	
Incidence of Pregnancy Complications (Maternal)*				
	12-24	**≥ 25**	**Total**	***p***
Pregnancy Complications *N*	40	9	49	
Pregnancy Complications (%)	24%	15.3%	21.6%	0.20
N Pregnancies	166	59	225	
*Excluding Spontaneous Preterm birth				
Incidence of Perinatal Complications (Neonates)*				
	12-14	**≥ 25**	**Total**	***p***
Neonatal Complications *N*	30	13	43	
Neonatal Complications (%)	17.4%	22.0%	18.6%	0.44
N Infants	172	59	231	
*Excluding IUGR and birth defects				

Table 2: *Incidence of Major Birth Defects, Neonatal Neutropenia at Birth and Pregnancy and Perinatal Complications for Maternal and Neonatal by Gestational Age at Initiation of Chemotherapy (in weeks)*

A total of 19 anomalies (8.2%) were diagnosed in this cohort by age 2 years. There was a significant difference in the incidence of birth defects when treatment began between 12-24 weeks GA when compared with >25, p=•05. One of these occurred in a family known to carry the autosomal dominant mutation for the same defect (father of child affected). Birth defects are further detailed in Supplemental Table 1, including the type of anomaly, GA at first treatment, treatment required, and neonatal age and status at latest follow up. Most of the birth defects were not life-threatening, aside from a single case of spina bifida, which likely occurred prior to initial chemotherapy exposure at 14•7 weeks GA.

Also in Table 2, the incidence of neonatal neutropenia was compared between groups and was not found to be significantly different when chemotherapy began at 12-24 weeks GA vs >25 weeks GA, p=•57 (Table 2). All infants born with neutropenia were preterm. Other neonatal complications were not significantly related to GA at first chemotherapy cycle, p=0.44. There was no significant difference in the incidence of maternal complications at delivery when chemotherapy began at 12-24 weeks GA vs >21-24 weeks GA, p=•20. Maternal and neonatal complications during pregnancy, delivery, or newborn period are described in Supplemental Table 2. The incidence of postnatal pediatric medical conditions; developmental, language and motor delays; and behavioral issues are compared in Table 3. These were not significantly related to the GA at first chemotherapy treatment. The types of maternal and neonatal complications during pregnancy, delivery, or newborn period are further described in detail in Supplemental Table 2. For each primary outcome, GA at first chemotherapy cycle was analyzed for a significant GA cut-point using recursive partitioning. The significant GA cut-point for birth defects was <17 weeks at first chemotherapy exposure.

This corresponded to a 3•9-fold increased risk of birth defects, OR =3•9 (95% CI 1•43, 10•9) (p=•008), if chemotherapy began at <17 weeks GA.

Incidence of Pediatric Medical Conditions				
	12-24	≥ 25	Total	*p*
Pediatric Medical Conditions*N*	56	21	77	
Pediatric Medical Conditions (%)	35.9%	43.8%	37.8%	0.39
N Infants	156	48	204	
Developmental/ Language or Motor Delay*N*	13	8	21	
Developmental/ Language or Motor Delay (%)	8.3%	16.7%	10.3%	0.11
N Infants	156	48	204	
Incidence of Behavioral Issues				
	12-24	≥ 25	Total	*p*
Behavioral Issues *N*	5	1	6	
Behavioral Issues (%)	3.2%	2.1%	2.9%	1.0
N Infants	156	48	204	

Table 3: *Incidence of Pediatric Complications after Birth including medical conditions, language and motor delays, or behavioral issues by Trimester at Initiation of Chemotherapy (in weeks)*

The significant cut-point for spontaneous preterm birth was 18 weeks GA, and 15 weeks GA for intrauterine fetal growth restriction. Odds ratios were: congenital anomalies, 16.6 weeks GA, OR=3.9 (95% CI 1•4-10•9), p=•008; PPROM/spontaneous preterm birth 18 weeks GA, OR=2•3 (95% CI 1•04, 4•86), p= •04; intrauterine growth restriction 15 weeks GA, OR=2•99 (95% CI 1•04, 8•6), p=•043.

DISCUSSION

As cancer occurs in only 1:1000 pregnancies, creation of an international cohort study of pregnant women diagnosed with cancer was warranted. Oncologists and obstetricians require long term follow up on mothers and children to best counsel newly diagnosed patients on the safest agents to use and safest time to begin in pregnancy, taking into account how long a delay can be tolerated by the mother. Multidisciplinary treatment of such patients requires the following questions to be asked:

1) After the first trimester of pregnancy is completed is any additional delay warranted to limit overall fetal exposure to chemotherapy if it does not compromise maternal prognosis?

2) Does it make a difference to the fetus to be exposed earlier in pregnancy when compared with a later GA? To date, there are no studies that identify the ideal time to begin chemotherapy after a diagnosis of cancer during pregnancy. In this observational cohort study, we analyzed pregnancy outcomes for mothers and neonates, as well as long-term neonatal health, after initial chemotherapy exposures began as early as 12 weeks GA and compared results with beginning chemotherapy at a later GA.

The placenta grows along with the fetus, weighing about one-sixth as much as the fetus at birth. Starting chemotherapy earlier in pregnancy may result in a lower birthweight due to decreased placental growth as an early effect of chemotherapy on placental development. Zemlickis reported IUGR as a consequence of chemotherapy exposure in utero in 1992 [15]. Intrauterine growth restriction, defined as birth percentile weight < 10%, was found in 20.3% of infants in this cohort, with no significant difference between starting chemotherapy between 12-24 weeks compared to after 25weeks. Using recursive partitioning, fetal growth restriction increased significantly when treatment began prior to 15 weeks GA. The intervillous space of the placenta originates as lacunae within the syncytiotrophoblast which anastomose with maternal capillaries filling with maternal blood at about 10 weeks' gestation. Early villous sprouting is initiated by

cells in regions of cytotrophoblasts and villous stroma with high proliferative activity. The number of cytotrophoblasts increases roughly 10-fold between the 13th and 15th week and term. Cytotrophoblast cells are recruited into syncytiotrophoblasts, which create attenuated protrusions called syncytial sprouts subsequently acquiring a vascularized stroma to become mesenchymal villi. Starting in the 9th week, tertiary stem villi lengthen by forming terminal mesenchymal villi, increasing the surface area available for transplacental exchange. These terminal extensions reach their maximum length in the 16th week [16]. In cases of fetal growth restriction, the placenta histologically exhibits compromised growth of villous trees, a smaller intervillous space, and a lower diffusive conductance and decreased total volumes and surfaces solely attributable to reduce linear growth of villi and capillaries [17, 18]. Chemotherapy exposure prior to achieving a maximum number of cytotrophoblasts or the villi achieving maximum length may result in deleterious effects on fetal growth. Maternal smoking, hypertension, diabetes, medications, stress, and the underlying cancer can impact fetal growth potential. A limitation of this study is the lack of consistent maternal smoking histories during pregnancy.

There were no significant differences in neutropenia or other neonatal complications. With longer neonatal follow up, no difference in medical conditions, developmental, language or motor delays, nor behavioral issues were identified according to GA at the initiation of chemotherapy.

Three percent of neonates in the general population are born with major congenital anomalies [19, 20]. Additional anomalies can be detected after birth; the incidence reaches 6% by 2 years and 8% by 5 years [20]. Current literature reports no increased risk of anomalies associated with second- or third-trimester use of cytotoxic agents [6, 7, 10, 17, 21-24]. Most cases describing chemotherapy use in pregnancy report the status of the neonate at birth, a few months or to one year of age. In this cohort, 7 infants were diagnosed with congenital anomalies at birth (3%). Twelve anomalies were diagnosed between 1 and 27 months of age for a total of 19 major anomalies among 232 infants (8•2%). Our higher rate when compared with other publications after chemotherapy use during pregnancy is likely due to a longer follow up and inclusion of congenital anomalies diagnosed at later ages. Our cohort data show a slightly higher rates of congenital anomalies when compared with the anticipated rates seen in the general population by age 2 years, (7•3%), but within the general population range of 8•2% by age 5 years. Using recursive partitioning, the delay of chemotherapy until 16.6weeks may significantly decrease the incidence of birth defects. This decision must be balanced against the maternal risks of delaying treatment. For each GA week that chemotherapy was delayed, incidence of birth defects decreased by 12% (data not shown). As shown in Supplemental Table 1, no birth defects were life threatening, and few of the children required long-term therapy. Parents should be informed of the anomalies that may be diagnosed if chemotherapy cannot be safely delayed until 16.6 weeks GA without compromising maternal health.

Aviles and colleagues reported detailed follow-up of 84 children exposed in-utero to chemotherapy in 2001 [21]. Neurological, intellectual, and visual-motor assessments performed by blinded physicians were no different for exposed children when compared with siblings and non-related controls. Amant et al. reported a on the development and cognitive performance of 70 children exposed to cancer treatment in utero. Children who exhibited delays were concentrated in the group delivered preterm [22, 24]. When 35 children exposed to chemotherapy in utero were compared with 22 children born to women with cancer who did not receive chemotherapy, there were no significant differences in cognitive skills, academic achievement, or behavioral competence. [23]. Current practice is to avoid chemotherapy during organogenesis in the first trimester. This study shows there may be additional benefit on fetal growth, congenital anomalies and the incidence of preterm birth with delaying the start of chemotherapy even later into the second trimester. This is the first analysis to examine exposures to chemotherapy in utero according to GA at the first maternal treatment, with both short- and long-term neonatal follow up data. The odds of intrauterine growth restriction increased when chemotherapy began by 15 weeks GA. The incidence of congenital anomalies was higher when chemotherapy began prior to 16.6 weeks GA. Odds of a spontaneous preterm birth increased significantly when chemotherapy began at 18 weeks GA. Other long-term medical issues for the neonate, developmental delays in language or motor skills, and behavior were not related to the GA at which chemotherapy began, nor were maternal complications of pregnancy aside from spontaneous preterm delivery. Although there is much variation in disease and in types/classes of chemotherapy used, to our knowledge, this is the only report to investigate neonatal and maternal consequences of chemotherapy exposures at various gestational ages, including exposures that occurred very early in gestation.

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SUPPLEMENTARY TABLES:

Supplemental Table 1*: Anomalies Listed with Details of Gestational Age at First Treatment, Age at which Anomaly Diagnosed, Treatment if Necessary and Age of Most Recent Neonatal Evaluation by Pediatrician/Specialist*

Major Birth Defect	GA treatment	Age birth defect diagnosed	Treatment	Age at most recent follow up (years) Medical concerns
Hydroureter, hydronephrosis	12.1	Suspected in utero at 20 weeks	Antibiotics for vesicoureteral reflux	3.4 grade 1V vesicoureteral reflux
Hemangioma multiple	14.3	2.2 months	None	6 years, Bronchospasm, Roseola Infantum
Plagiocephaly	14.4	3.4months	Helmet	Resolved by 10 months
Spina Bifida	14.7	Suspected in utero at 16 weeks	Neurosurgery at 6 months: no evidence of tethered cord or Chiari malformation	7.8, Grade II Vesicoureteral reflux, urinary tract infections, on ditropan, motor age 3 months behind, Reactive Airway Disease, retinopathy, milk protein allergy, gastroesophageal reflux
Syndactyly 2 fingers	14.5	At birth	Surgery	18 years no medical issues/limitations
Hypospadias	15.1	At birth	Surgery	2.5 , Undescended testis
Plagiocephaly	15.1	6 months	Helmet	6.6, Resolved,9 months of age, No medical issues
Hemihypertrophy	15.3	22 months	Physical therapy	8.75Physical therapy for motor delay, tracheomalacia, Mongolian spot
Blepharoptosis	16.6	3 weeks	None	6, Resolved by 4 months, Articulation delay, Asthma, multiple hyperpigmented lesions, laryngomalasia, brief bell's palsy, head deformity with muscle tightness
Pyloric Stenosis	16.7	1 month of age	Surgery at 6 weeks of age	8.6no medical issues
Cleidocranial dysostosis	18.0	6 days of life, parent has same Autosomal Dominant condition,	None	
Right ureteralpelvic junction obstruction, hydronephrosis	18.9	Suspected prenatally at 20weeks	None	8.3years, right moderate hydronephrosis, Urinary tract infection
Plagiocephaly	19.0	4 months	Helmet	9, Resolved, 1 year of age, gastro esophageal reflux
Epibulbar dermoid cyst	20.0	13.5 months	17.7 months surgically removed	9 years of age, Articulation delay
Hydronephrosis	21.0	Suspected prenatally at 21weeks	None	2 year, no medical issues
Thyroglossal duct cyst	22.1	28.6 months	Surgery at 31.6 months	36months no medical issues
Right ureteralpelvic junction obstruction, hydronephrosis	23.3	Suspected prenatally at 24 weeks	Pyeloplasty at 1 month of age	6, Gross motor delay, gastroesophageal reflux, urinary prophylaxis, Sensory issues

Muscular ventricular septal defect	24.9	Murmur heard age 2 months during fever, small VSD found, asymptomatic		No treatment
Congenital Scoliosis	27.1	Diagnosed 4 months	Wears Brace	5.1 years, expressive speech delay, Otitis media with tubes placed, Gross motor delay

Supplemental Table 2: *Complications for mother at birth, at time of delivery or pediatric follow up for newborn*

- Perinatal complications for the mother during pregnancy and delivery, at birth (perinatal) or during pediatric follow up for the newborn Gestational Age at Initiation of Chemotherapy: 12-14 weeks.

Perinatal Complications - Maternal	**Gestational Age at Delivery (weeks)**	**Perinatal Complications – Neonatal**	**Pediatric Medical Conditions, Developmental Delays or Behavioral Issues**
Preeclampsia	30.1	Apnea of prematurity, Respiratory Distress Syndrome	IgA deficiency, phimosis, constipation, gastroesophageal reflux
Preeclampsia	34.7		Non-ossifying fibroma of femur, low Body Mass Index sees nutritionist
	36.1		Asthma
Postpartum Depression	36.0		
Placental Abruption	33.3		Clogged tear duct
	38.4		Gastro esophageal reflux
Pyelonephritis, ureteral obstruction and Clostridium.difficile	34.0		
	35.3		Asthma
Chorioamnionitis twins	29.6		Eczema in 1 twin
	32.1		Asthma, pedal warts
	35	Hypoglycemia	
	36.3		Asthma, hydrocele

	31.1	Anemia required transfusion; hyaline membrane disease; hypoglycemia; apnea and bradycardia	
	31.6		Motor delay at 10 months
	27.0		Strabismus in each twin
	35.6	Transient tachypnea of the newborn	
Anemia	36.6		
	38.0		Gastro esophageal reflux, eczema
	37.3		Sacral dimple, surgery for spinal cyst
	37.4	Ventriculomegaly noted at 16 week fetal ultrasound, CT (computed tomography) scan 2 months of age showed prominence of lateral ventricles with no other abnormalities, no intervention required	Attention deficit hyperactivity disorder, educational and behavioral delays
Postpartum hemorrhage	40.0		
	40.0		Seborrhea of infant
	37.9		Bronchiolitis, recurrent otitis media Torticollis, gastroesophageal reflux
Depression	37.7		
	38.4		Gastroesophageal reflux, asthma, food allergies, dermatitis

- Perinatal complications for the mother during pregnancy and delivery, at birth (perinatal) or during pediatric follow up for the newborn Gestational Age at Initiation of Chemotherapy: 15-16 weeks.

Perinatal Complications - Maternal	Gestational Age at Delivery	Perinatal Complications - Neonatal	Pediatric Medical Conditions, Developmental Delays or Behavioral Issues
	36.7		Strabismus, hemangioma
	37		Gastroesophageal reflux, asthma, contact dermatitis
	36.1	Sclerosis for lymphatic malformation in neck	Gastroesophageal reflux
	33.4	Apnea and bradycardia, weight loss	
	36.3	Pustular rash at birth, resolved by 72 hours, hyperbilirubinemia, laryngomalacia	Bell's palsy, asthma, hyperpigmented lesions no other criteria for neurofibromatosis
	34.6	Lymphopenia	Fine motor delay, occupational therapy, normal by age 3 years
Deep Vein Thrombosis	36.3		Articulation problems- receiving speech therapy
	39.7		Articulation issue, referred for speech-resolved within 1 year
	38.6		Low Body Mass Index, eczema
	33.6		Asthma
	36.9	Tracheomalacia	

- Perinatal complications for the mother during pregnancy and delivery, at birth (perinatal) or during pediatric follow up for the newborn Gestational Age at Initiation of Chemotherapy: 17-18 weeks.

Perinatal Complications Maternal	Gestational Age at Delivery	Perinatal Complications - Neonatal	Pediatric Medical Conditions, Developmental Delays or Behavioral Issues
GDM (gestational diabetes mellitus)	35.9		
Superficial vein phlebitis			
	29.6		Vulvovaginitis
GDM	35.2		
Preeclampsia, postpartum hemorrhage	34.7		
	37.1	Hyperbilirubinemia	
	34.3	Respiratory distress syndrome	
Renal colic, GDM	36.6		
Fractured coccyx	37.6	Hypoglycemia	Colic, chronic benign neutropenia at 2 years of age, recurrent epistaxis. Mild left upper lid ptosis, runs in family
Anemia, GDM,	34.1	Hypoglycemia	

postpartum depression			
	38.9		Hashimoto's thyroiditis, vitiligo age 7
Postpartum depression when began radiation	39.0		
	38.7		Respiratory syncytial virus, bronchiolitis at 16months
	39.1		Vitiligo

- Perinatal complications for the mother during pregnancy and delivery, at birth (perinatal) or during pediatric follow up for the newborn Gestational Age at Initiation of Chemotherapy: 19-20 weeks.

Perinatal Complications – Maternal	Gestational Age at Delivery	Perinatal Complications – Neonatal	Pediatric Medical Conditions, Developmental Delays or Behavioral Issues
	36.9		Asthma, Attention deficit hyperactivity disorder
Breech, oligohydramnios	36.4		Attention deficit hyperactivity disorder age 7, no treatment by age 10
Oligohydramnios	37.4		Gastroesophageal reflux
	34.6		
	35.6`		Bronchiolitis, asthma, iron deficiency anemia
	32.4 twins	Each mild respiratory distress syndrome, 1 with oral thrush, apnea of prematurity	Asthma for each twin
Anemia, transfused	39.4		Mild articulation issues
	36.6	Hyperbilirubinemia	
	35.0	Apnea of Prematurity	Gastroesophageal reflux
	38.1		Bronchiolitis
	37.0	Hyperbilirubinemia	Gastroesophageal reflux
Chorioamnionitis	38.7		Gastroesophageal reflux
	38.3		Gastroesophageal reflux
Pregnancy induced hypertension	34.3		Failure to thrive 18mths, resolved by 34
	38.0		Mild speech delay at 16 months, resolved by 38months
Postpartum depression	39.3		
	34.4		Asthma
	36.9	Hypoglycemia, required brief respiratory support	
	38.3		Pneumonia
Postpartum hemorrhage	40.1		
	34.6		Vaginitis

- Perinatal complications for the mother during pregnancy and delivery, at birth (perinatal) or during pediatric follow up for the newborn Gestational Age at Initiation of Chemotherapy: 21-24 weeks.

Perinatal Complications - Maternal	Gestational Age at Delivery	Perinatal Complications - Neonatal	Pediatric Medical Conditions, Developmental Delays or Behavioral Issues
Placental abruption	28.3	Anemia requiring transfusion	Gastroesophageal reflux

chorioamnionitis			
Anemia requiring transfusion	33.9	Fetal Arrhythmia	
	40.3		Single hemangioma, Fine motor delay
	38.9		Eczema, food allergies
Postpartum hemorrhage	36.6	Leukopenia	Gastroesophageal reflux , sensory issues and anxiety
Hyperemesis	36	Failure to thrive	Expressive and receptive language delay, sensorineural hearing loss
Oligohydramnios and poor biophysical profile	27.7	Anemia of prematurity	Expressive speech delay, Gastroesophageal reflux, lumbar lordosis
	36.6	Neutropenia, resolved by 7 months, normal immune system cleared by pediatric immunologist	
	38.1		Asthma
Placenta Previa, bleeding; postpartum depression	33.6	Sepsis, Respiratory distress syndrome, anemia	
	39.0		Eczema, GERD
Cesarean Section wound cellulitis	36.0		Hand, foot, mouth disease, gastroesophageal reflux
	39		Reactive Airway Disease
Placental abruption, postpartum depression	37.9		
Postpartum Depression, anemia	36.7		
Postpartum Depression	37.7		
	38.6		1 twin Asperger's, Tourette's, Obsessive Compulsive Disorder, fraternal twin no behavioral or developmental issues
HELLP Syndrome	35.3		
Group B Strep bacteriuria, Gestational diabetes	37.4		
	40.9		Speech delay
Placenta Previa, uterine atony, postpartum hemorrhage	37.3		
	40.9		Recurrent Otitis media
Postpartum hemorrhage	38		Recurrent Otitis media

	36.7		Asthma, otitis media; mild expressive speech delay, delay of fine motor skills
	36.4		Gastroesophageal reflux
Postpartum depression	30.4	Twins, each with apnea	Each twin sees vision specialist
	36.7		Asthma, otitis media, childhood obesity, fine motor and expressive language delay
	36.3	Respiratory distress syndromess	

- Perinatal complications for the mother during pregnancy and delivery, at birth (perinatal) or during pediatric follow up for the newborn Gestational Age at Initiation of Chemotherapy: After 25 weeks

Perinatal Complications - Maternal	Gestational Age at Delivery	Perinatal Complications - Neonatal	Pediatric Medical Conditions, Developmental Delays or Behavioral Issues
	38.3	Hypoglycemia	Urticaria, Osgood-Schlatter disease in knees
	38.0	Jaundice	
	33.6	Hypoglycemia	
	39.0		Gastroesophageal reflux
	34.9	Respiratory distress syndrome, day 1 of life hypoxic episode and tachypnea x 24 hrs. prior to intubation, 2 spontaneous pneumothoraxes, seizures prompted Magnetic Resonance Imaging which showed periventricular leukomalacia	Developmental delay; legal blindness
	28	Respiratory distress syndrome, anemia of prematurity	Bronchiolitis
	34.1	Apnea, hypoglycemia, gastritis	
	34.4		Oral motor issues & feeding issues-speech therapy
Retained placenta	33.9		
	35.1	Respiratory distress syndrome	
	37.3	Apnea	Speech delay, gastroesophageal reflux, Mongolian spot and nevus
Retained placenta, hemorrhage	39.6		
Postpartum hemorrhage	36.0		
	38.9		Bronchitis
Postpartum depression	39.3		Speech Delay Recurrent otitis media
	36.9		Scoliosis; premature adrenarche
	33.4		Eczema
Anemia requiring transfusion at delivery	35.6	Hyperbilirubinemia	Recurrent otitis media, upper respiratory infection
Gastroenteritis, Upper respiratory	38.9		Underweight

infection			
Deep vein thrombosis, pneumonia, anemia requiring transfusion at delivery	31.0	Respiratory distress syndrome, anemia of prematurity	
	33.0	Neutropenia, anemia, narcotic withdrawal	
	33.9	Respiratory distress syndrome	Food allergies, eczema, asthma, hemangioma on back, unilateral hydrocele; asthma
	37.6		Attention deficit hyperactivity disorder, reading support
	34.3		Gastroesophageal reflux
	34.6		Referred for expressive speech therapy 18-24months, resolved by age 36months
	35.6	Hypoglycemia	
	37.7		Gastroesophageal reflux
	37.7		Recurrent otitis media
Gestational diabetes	38.1		
	36.9		Exercise induced asthma; sleep apnea, speech therapy
	39.3		Multiple food allergies; atopic dermatitis
	37.7		Asthma
Gestational diabetes	37.7		Eczema
	35.4		Corneal abrasion
	39.7		Single hemangioma behind knee
	34.7		Speech therapy; constipation