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Authors: Beata Pawlus, Jerzy Zwolinski, Urszula Koneczna, Grzegorz Pawlus, Agnieszka Kordek

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Neonatal outcomes for women diagnosed with cancer during pregnancy — single-center study

Beata Pawlus^{1,2}, Jerzy Zwolinski^{1,2}, Urszula Koneczna^{1,2}, Grzegorz Pawlus³, Agnieszka Kordek⁴

¹Faculty of Medicine, Lazarski University, Warsaw, Poland

²Specialist Hospital of Holy Family, Warsaw, Poland

³Department of Physical Education, Academy of Physical Education and Sport, Gdansk, Poland

⁴Department of Neonatology and Neonatal Intensive Care Pomeranian Medical University in Szczecin, Poland

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Corresponding author:

Agnieszka Kordek

Department of Neonatology and Neonatal Intensive Care Pomeranian Medical University in Szczecin, 2 Siedlecka St., 72-010 Police, Poland; phone: 501 197 941

e-mail: agnieszka.kordek@pum.edu.pl

ABSTRACT

Pregnancy complicated by cancer is one of the most serious challenges of modern perinatology. The increasing number of cancers diagnosed and treated during pregnancy requires a multidisciplinary approach to optimize the treatment of the person who is pregnant and deliver a healthy child. The aim of the study is to analyze the course of the neonatal period in children of mothers suffering from cancer during pregnancy, treated in a specialist hospital for women and children. Being diagnosed with cancer during pregnancy significantly increases the risk of premature delivery, prematurity and intrauterine growth restriction. Our own observations show no significant differences during the neonatal period in children of mothers suffering from a malignant tumor during pregnancy compared to children of healthy mothers. This applies to both full-term and premature babies. Modern treatment of malignant tumors during pregnancy seems to be safe for the fetus and newborn. It is optimal to conduct oncological, obstetric and neonatological treatment in one center. It seems advisable to conduct long-term follow-up observations in children of pregnant people with cancer. Since the described groups of patients and their newborns are small and

heterogeneous, in order to develop appropriate standards, it is recommended to report these cases to central registers.

Keywords: newborn; pregnancy; cancer

INTRODUCTION

Pregnancy complicated by cancer is one of the most serious challenges for obstetricians and neonatologists. This leading to a difficult situation related to the care of the so-called "extended patient", *i.e.*, a newborn and the pregnant women.

“Pregnancy-related cancers” was defined as a diagnosis of malignancy from the time of pregnancy until 12 months after delivery. Most cases are diagnosed in the postpartum period, but the number of women diagnosed with cancer during pregnancy is steadily increasing. This is due to the increase in the incidence of malignant neoplasms in the entire population and the older age of pregnant women. Age is believed to be the main risk factor for developing cancer during pregnancy. The incidence of malignant neoplasms has increased in the female population over the last three decades by about 60%. It is estimated that cancer may occur in up to 1 in 1000 pregnant people worldwide [1].

A pregnant women diagnosed with a malignant tumor requires special multidisciplinary care (gynecologist–obstetrician, surgical oncologist, clinical oncologist/chemotherapist, psychologist, dietician, neonatologist, lactation consultant, physiotherapist) and a clear plan of therapeutic management with a presentation of risks and threats. For most patients, the main worry is fear for their own life and health, as well as the prognosis for the health and development of their child. The optimal solution is the possibility of treating the patient in one center, where complicated pregnancy can be managed, the patient can be operated on and treated with chemotherapy, the newborn can receive help adequate to the stage of pregnancy, and the women can receive lactation and psychological care. If it is necessary to terminate the pregnancy prematurely (usually due to the condition of the patient and continuation of their treatment, the newborn and mother can be treated in one center, which allows for at least limited but possible contact between parent and child. The newborn may, in addition to highly specialized neonatological treatment, receive modern nutritional treatment in the form of breast milk from a milk bank for the period of stabilization of the general condition and/or the mother's possible return to breastfeeding [2]. Such an interdisciplinary approach reduces the level of anxiety in the patient, increases the level of safety and, above all, positively affects the long-term effects of treatment for both the pregnant women and the child in this clinically and psychologically difficult situation [3, 4].

It should be remembered that therapeutic management in pregnancy complicated by malignancy should consider not only medical indications, but also the patient's preferences and important ethical and religious aspects, including decisions to continue the pregnancy in the context

of a threat to health and life. Studies show that termination of pregnancy does not improve prognosis in patients diagnosed with malignancy during pregnancy. The International Network on Cancer, Infertility and Pregnancy (INCIP) recommends oncological treatment while maintaining pregnancy [5, 6], although we find retrospective cohort studies showing that, in the group of women diagnosed with cancer, decisions about abortion/induced miscarriage were more frequent than in the control group [7]. The prognosis for patients diagnosed with cancer during pregnancy is similar to that for non-pregnant women at the same stage of cancer. Appropriately selected therapy does not pose a risk to the fetus and further development of the child, nor does it diminish its effectiveness [5, 8].

Pregnancy is not a contraindication to anticancer surgical treatment [8]. Most malignant solid tumors require surgical treatment. Both the procedure and the anesthesia may have adverse effects on the fetus. Anesthetics do not increase the risk of congenital defects, but their use in the first trimester of pregnancy carries the risk of miscarriage. It is recommended to perform operations in the II and III trimesters of pregnancy. After the 24th week of pregnancy, the well-being of the fetus should be monitored during the procedure, and the patient should be warned about the possibility of performing a cesarean section in the event of a threat to the life of the child [3, 4, 6].

The use of cytostatic drugs during the first trimester of pregnancy is associated with a high risk of fetal damage, but most cytotoxic drugs can be safely used in the second and third trimester of pregnancy, considering the specificity of the pregnancy period (larger plasma volume, lower albumin concentration, altered renal and hepatic function). Therefore, chemotherapy can be used in the second and third trimesters of pregnancy, but usually not longer than 34–35 weeks of pregnancy, with a 3-week break in therapy before the planned termination of pregnancy (if there is no need for early termination of pregnancy due to maternal indications). This is dictated by the limitation of the effect of drugs on the condition of the newborn, because almost all cytostatic drugs cross the placental barrier. The decision to start radiotherapy in pregnant women should be made only in special cases, as in principle it is not used in the treatment of pregnancy-related cancers [5, 6, 9].

Childbirth in a pregnancy complicated by malignant tumor should, if possible, take place as in healthy individuals, by natural means. After a natural birth, oncological treatment can be started faster — chemotherapy after a natural delivery is possible almost immediately, and after an uncomplicated caesarean section, after about a week. The decision to perform caesarean section may be made based on obstetric or oncological indications [6, 10–12]. Breastfeeding of a newborn by a pregnant woman suffering from a malignant tumor during pregnancy is possible. The decision not to start or stop breastfeeding is always up to the patient. However, it should be remembered that breastfeeding is contraindicated during radiotherapy and chemotherapy, which is possible after birth. Cytostatics pass into breast milk, causing leukopenia. Breastfeeding can be started two weeks after the end of chemotherapy [5, 13].

Cancer epidemiology in pregnancy varies slightly from region to region. The reports mention various cancers diagnosed in pregnant women: breast, cervical and ovarian, thyroid, colorectal, hematopoietic system, Hodgkin's lymphoma, melanoma, and brain tumors. Breast cancer is the most common malignancy diagnosed in pregnancy worldwide. Around 10,000 people worldwide suffer from breast cancer during pregnancy every year [1, 5, 13, 14]. Breast cancer in pregnant women is usually diagnosed at a more advanced stage than in the non-pregnant population. The growing lump in the breast is treated as a physiological response of the glandular tissue to hormonal changes associated with pregnancy. Women in general, but also doctors, do not realize that breast cancer can occur in a young pregnant woman. Diagnosis in pregnant women is delayed by 2–7 months from the moment the first symptoms appear. Delaying the diagnosis by six months results in an increase in the number of patients with regional lymph node metastases by over 5% [5, 13, 14]. Breastfeeding is possible and safe after the diagnosis and treatment of breast cancer, although the literature in this area is scarce and is based on only a few groups of patients. Breastfeeding counseling and planning are key factors in maintaining and prolonging lactation in women with breast cancer. However, despite this, about half of breast cancer patients choose not to breastfeed or express their own milk. Breastfeeding usually involves a healthy breast. The reasons for not trying to feed from an affected breast are usually difficulty in suckling, reduced milk production and breast pain. There are no differences in the frequency of recurrence of the disease in the group of women who are breastfeeding and those who give up breastfeeding [5, 13].

The aim of the study was to summarize the ten-year own observations of neonatal outcomes for women diagnosed with cancer during pregnancy.

MATERIAL AND METHODS

A retrospective analysis covered the course of the neonatal period of children born to pregnant women suffering from malignant tumors over 10 years (2012–2021) in a multi-specialty reference center (Specialistic Hospital of the Holy Family, Warsaw, Poland). During this period, 52,088 deliveries took place in the hospital. A total of 399 cases of tumors during pregnancy were diagnosed, including 379 benign tumors and 20 cases of cancers. Pregnant women suffering from malignant cancer, who were treated oncologically during pregnancy and gave birth to newborns accounted for 0.04% of all patients giving birth in the hospital in this period. It is adequate in relation to the data from the literature, *i.e.*, 0.02–0.1% of all pregnancies [1]. The Specialist Hospital Holy Family in Warsaw is a reference center for the region, focused on comprehensive diagnostics and the treatment of women and their children. It has modern departments in its structure, including obstetrics, neonatology, pediatrics, oncological gynecology, oncological surgery, clinical oncology and a regional breast milk bank. In addition to specialist neonatal care with the possibility of

intensive care and treatment at the neonatal pathology ward, further care and follow-up at the pediatric ward is possible.

The source of information was medical records. Each case of cancer diagnosed during pregnancy was analyzed. The small size of the group and its heterogeneity limited the possibility of statistical analysis.

RESULTS AND OVERVIEW

Among the twenty analyzed cases, seven cases of breast cancer, five cases of thyroid cancer and a single case of cervical cancer, ovarian cancer, Hodgkin's lymphoma, lymphoblastic leukemia, colorectal cancer, anal cancer, sarcoma and fibromatosis desmoid were diagnosed and treated. The patients' age, oncological diagnosis, course of pregnancy, method of delivery, fetal age, birth weight of newborns, and course of the neonatal period are shown in Table 1. The age of the patients ranged from 19 to 36 years (mean 30.5 years). In our study group, 12 newborns (60%) were born by caesarean section. In this hospital, the caesarean section rate in the entire patient population is quite high at 50%. Oncological indications for the caesarean section were observed in the following five cases: cervical cancer and advanced neoplastic processes in patients with ovarian, rectal, sigmoid, and Hodgkin's lymphoma.

Although, cervical cancer is one of the most common in women of reproductive age, only one of the women in our study had stage IIA1 cervical cancer. Due to the previous caesarean section and the oncological condition, the pregnancy was terminated by caesarean section at the time of delivery (41 weeks of gestation). Radical surgical treatment was performed after the birth of the child [14].

Additionally, one case of ovarian cancer occurred among our patients. The pregnancy was terminated prematurely by caesarean section due to oncological indications. Radical surgical treatment was performed after the child was extracted [15].

Newborns of mothers with pregnancy-related cancer were born at a gestational age of 24 to 41 weeks, the mean 36.1. In total, 7/20 newborns were born prematurely — 35% (Tab. 1). In the Polish population, the percentage of prematurity in those years was between 6-7%. Late premature babies — 5/7, 2 were born below 32 weeks gestation (29 and 24). Both mothers of the most immature children died in the first year after delivery — they presented the most advanced cancer process, and the decision to end pregnancy prematurely was dictated by the mothers' health condition. A significantly increased percentage of prematurity in the group of newborns born to mothers with cancer during pregnancy, consistent with the reports of other authors, is iatrogenic. The decision to terminate pregnancy prematurely is dictated by oncological indications and the need to treat the mother [1, 16–19]. In the study "Pregnancy and Cancer: the INCIP Project" published in 2020, based on the data register from the International Network on Cancer, Infertility and

Pregnancy (INCIP) database, the authors report up to 47% prematurity in the group of newborns born to mothers with malignant tumors during pregnancy, of which one third are newborns born before 34 weeks of gestation [6] (Tab. 1).

Among the analyzed newborns, 5/20 were born with a low birth weight (LBW) below 2500 g, including one newborn with a very low birth weight (VLBW) and one with an extremely low birth weight extremely low birth weight (ELBW). The authors point out the risk of fetal growth retardation intrauterine growth retardation (IUGR) and fetal hypotrophy (SGA-small for gestational age) in the group of newborns of mothers with cancer during pregnancy, especially when the pregnant woman is treated with chemotherapy [6, 20, 21]. We suggest ensuring the careful monitoring of the well-being of the fetus and the decision to complete the pregnancy at 35–36 weeks gestation as the safest for a newborn at risk of IUGR [22, 23].

Only two newborns in our group could be included in the SGA group. One of them was diagnosed with a congenital heart defect — ventricular septal defect (VSD), which means that the cause of hypotrophy was not fully attributed to the mother's cancer. The second case is a premature baby, 36 weeks gestation, mother with recurrent desmoid disease, recurrence of the disease during pregnancy, removal of a tumor of the left seventh rib and the latissimus dorsi muscle in the second trimester of pregnancy, maternal hypertension and chronic use of opioids for analgesic treatment. The causes of hypotrophy seem to be complex in this clinical situation. However, the register data of the International Network on Cancer, Infertility and Pregnancy (INCIP) show that up to 21% of newborns born to mothers with cancer during pregnancy may be born too small for their gestational age (SGA) [6].

Two newborns in the analyzed group were diagnosed with a heart defect. In both cases, heart defects were detected in the form of a defect in the interventricular septum, without significant hemodynamic disturbances and the need for intervention. Few authors have tried to search for a relationship between oncological treatment during pregnancy and heart defects in the fetus and newborn. Most pregnant cancer patients undergo chemotherapy treatment in the second or third trimester of pregnancy, after the period of organogenesis, and such a relationship has not been proven [23]. However, there are still numerous studies evaluating the impact of chemotherapy and/or growth factor support during pregnancy on fetal development, in a broader sense than just the risk of development defects. Although the results are reassuring, the number of cases remains understandably limited, and continuous surveillance of patients and their newborns is warranted [24, 25]. One of the newborns was diagnosed with a skull bone defect and one with a cavernous hemangioma. A review of the literature does not indicate such cases; therefore, these diagnoses seem to be unrelated to maternal cancer.

The length of neonatal hospitalization depended on their maturity and the resulting problems of prematurity. Full-term infants (n = 13) were usually discharged between the third and fifth day of

life (n = 11), which is the standard adopted in our hospital. One neonate born by caesarean section for obstetric reasons after the end of the 37th week of pregnancy was discharged after 19 days for reasons unrelated to maternal breast cancer treated surgically in the first trimester of pregnancy. Due to perinatal complications (baby–maternal transfusion syndrome, severe anemia, perinatal asphyxia, IUGR), the child required treatment at the Neonatal Intensive Care Unit (NICU) for several days. Another newborn born by caesarean section due to deep vein thrombosis in the mother after the end of the 37th week of pregnancy was discharged after 10 days due to neonatal complications (pneumonia, pneumothorax, arrhythmia). The child required treatment with mechanical ventilation for five days in the NICU.

Three more newborns required treatment in the NICU: a newborn with ELBW (500 g) born at 24 weeks of gestation and a newborn born at 29 weeks of gestation, as well as a newborn born at 34 weeks of gestation who developed respiratory distress syndrome (RDS) II degree. These five children required respiratory support. No newborns died.

The course of the neonatal period of children of mothers suffering from malignant neoplasm during pregnancy, was completely uncomplicated in most children. Out of the thirteen full-term newborns, one was diagnosed and treated with congenital pneumothorax, and one was treated with severe congenital anemia during the mother–child transfusion syndrome. There was no association with maternal cancer. The remaining full-term newborns did not present any disturbances in the neonatal period. In all prematurely born newborns, typical and appropriate disorders were observed, ranging from mild adaptation disorders in the so-called late premature infants to serious diseases associated with extreme prematurity (details in Tab. 1) — as in newborns of mothers not suffering from cancer during pregnancy. In the few available studies analyzing the course of the neonatal period and infancy, the authors indicate no differences during the neonatal period of children of pregnant mothers with cancer compared to children of healthy mothers [11]. The most common complication in the perinatal period associated with the use of chemotherapy in the patient is myelosuppression of various degrees, which in most cases is transient [23]. Follow-up of children of mothers suffering from cancer during pregnancy in terms of cognitive disorders shows that the disorders result only from prematurity, and they are comparable to children born in the same period of pregnancy without chemotherapeutic treatment — no differences between the groups were found. The cognitive development of children of mothers with cancer should be considered undisturbed [23, 26]. This is confirmed by our own observations during routine examinations in the outpatient clinic.

CONCLUSIONS

Being diagnosed with cancer during pregnancy significantly increases the risk of premature delivery, prematurity and intrauterine growth restriction (IUGR). However, our own observations

show no significant differences during the neonatal period in children of pregnant mothers with malignant tumors compared to children of healthy mothers. This applies to both full-term and premature babies. The treatment of malignant tumors during pregnancy seems to be safe for the fetus and newborn. It is optimal to conduct oncological, obstetric and neonatological treatment in one center. It seems advisable to conduct at least several years of follow-up in children of pregnant mothers with cancer. Since the described groups of patients and their newborns are small and heterogeneous, in order to develop appropriate standards, it is recommended to report these cases to the INCIP registry.

Article information and declarations

Data availability statement

All data available from the authors.

Ethics statement

{typ artykułu wymaga podania, nie może być “not applicable”}

Author contributions

Beata Pawlus: conception, assumption article, draft revision; Jerzy Zwolinski: aquisition of data, assumption; Urszula Koneczna: aquisition of data; Grzegorz Pawlus: analysis and interpretation of data, article draft; Agnieszka Kordek: draft revision, corresponding author.

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Conflict of interest

None.

Supplementary material

None.

Table 1. The course of pregnancy and the neonatal period

Mother's age [years]	Parity G/P	Diagnosis	Week of gestation	The course of pregnancy	Mode of delivery	Birth weight [g]	APGAR 1'/5',	The course of the neonatal period, hospital stay
N S	2 6	I/I	Breast cancer	37	After mastectomy at 25 weeks of gestation, during chemotherapy,	Cesarean	3757	10/10/10 Healthy newborn Cavernous hemangioma No complications

					failed induction of labor				4 days
I O	3 4	I/I	Breast cancer	39	After mastectomy, during chemotherapy, state after CS	Vagi nal	318 5	10/ 10/ 10	Healthy newborn No complications 3 days
M R	3 6	II/II	Breast cancer	40	Invasive cancer, diagnosis in the first trimester, no consent to treatment, thrombocytopenia	Vagi nal	286 0	10/ 10/ 10	Healthy newborn No complications 3 days
E W	3 2	III/I I	Breast cancer	37	After mastectomy at 24 weeks of gestation, during chemotherapy	Vagi nal	335 0	10/ 10/ 10	Healthy newborn Hyperbilirubinemi a phototherapy typical course 6 days
H K	3 6	II/II	Breast cancer	37	After mastectomy in the first trimester, GDMG1, IUGR, placental failure, fetomaternal shunt, depression; no consent to treatment chemotherapy,	Cesar ean	243 0	3/2/ 2	Perinatal asphyxia, baby-maternal transfusion syndrome, congenital anemia, hepatosplenomegal y, thrombocytopenia, neutropenia, cholestasis NICU 19 days
M K	3 5	IV/ III	Breast cancer	36	After a mastectomy in the first trimester, no consent to treatment chemotherapy, state after CS	Cesar ean	284 0	10/ 10/ 10	Prematurity, adaptive breathing disorders, HFNC 1 day typical course 5 days
P W	3 1	I/I	Breast cancer	40	Before oncological treatment	Vagi nal	362 5	10/ 10/ 10	Healthy newborn No complications 3 days
M L	2 5	II/I	Thyroid cancer	39	Condition after strumectomy, oligohydramnios	Vagi nal	267 5	10/ 10/ 10	VSD, hypotrophy, hyperbilirubinemia -phototherapy typical course 5 days
P B	3 5	III/I I	Thyroid cancer	38	Condition after strumectomy	Vagi nal	403 6	10/ 10/ 10	Healthy newborn No complications 3 days
K D	2 9	III/I	Thyroid cancer	38	Condition after strumectomy, Pelvic position of	Cesar ean	335 5	10/ 10/ 10	Healthy newborn No complications 3 days

					the fetus; GDMG2, PROM				
M S	3 0	II/I	Thyroid cancer	39	Condition after strumectomy,	Vaginal	3580	10/10/10	Healthy newborn No complications 3 days
M P	3 4	I/I	Thyroid cancer	37	Condition after strumectomy, deep vein thrombosis, polyhydramnios	Cesarean	3325	8/10/10	Pneumonia, respiratory failure, pneumothorax, Mechanical ventilation, cardiac arrhythmias NICU 10 days
I K	2 8	III/I I	Cervical cancer	41	Diagnosis II trimester, anemia; surgical treatment after childbirth; State after CS Oncological indications for CS	Cesarean	3024	10/10/10	Skull bone defect, neonatal period without complications 5 days
M B	2 3	I/I	Ovarian cancer	34	CS with removal of the appendages and greater omentum, the need for treatment Oncological indications for CS	Cesarean	2290	8/8/8	Healthy newborn Hyperbilirubinemia-phototherapy, typical course 10 days
B D	2 9	II/I	Hodgkin lymphoma	34	During chemotherapy, the need for further treatment Oncological indications for CS	Cesarean	2736	10/10/10	Prematurity, respiratory failure, RDS II, NICU 5 days
S D	1 9	I/I	Lymphoblastic leukemia, bilateral breast and ovarian tumors, mediastinal changes	24	Disseminated neoplastic process, diagnosis in the second trimester, postpartum chemotherapy, death in the first year	Vaginal	500	2/2/4	Extreme prematurity, respiratory failure, circulatory failure, PDA, IVH II, convulsions, late onset sepsis, BPD, ROP II, right ovarian cyst NICU 141 days
K M	2 8	II/II	Colorectal (sigmoid) cancer, metastases to the ovaries and liver, infiltration of the cervix,	29	Disseminated neoplastic process, palliative chemotherapy, low gastro-intestinal obstruction at 29 weeks gestation, single-barrel end stoma during CS, death in the first	Cesarean	1490	9/10/9	Prematurity, respiratory failure, hyperbilirubinemia-phototherapy NICU 44

			right parametrium and paravagina		year Oncological indications for CS				
JZ	3 4	II/II	Anal cancer	35	Operation in the 17 th week; depression, the need for further treatment Oncological indications for CS	Cesarean	2540	10/ 10/ 10	Prematurity, VSD, perinatal adaptation disorders, nCPAP 5 days
KK	3 2	III/I I	Sarcoma	37	Condition after chest reconstruction, GDMG2, PROM	Cesarean	3165	10/ 10/ 10	Healthy newborn No complications 3 days
PS	3 4	III/I II	Recurrent desmoid tumors	36	Relapse in pregnancy; removal of the tumor of the 7 th rib and the latissimus dorsi muscle in the 2 nd trimester — (fibromatosis desmoid-type), state after CS, FGR <u>I st {1st? I degree?}</u>	Cesarean	2025	10/ 10/ 10	Prematurity, hypotrophy, mild opioid withdrawal syndrome 11 days

G/P — gestation/parturition; GDMG — gestational diabetes mellitus; IUGR — Intrauterine growth restriction; FGR — fetal growth restriction; PROM — premature rupture of membranes; CS — cesarean section; VSD — ventricular septal defect; RDS — respiratory distress syndrome; PDA — patent ductus arteriosus; IVH — intraventricular hemorrhage; ROP — retinopathy of prematurity; BPD — bronchopulmonary dysplasia; NICU — Neonatal Intensive Care Unit; HFNC — high flow nasal cannula; nCPAP — nasal continuous positive airway pressure

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