4-6-2020

Effects of Maternal Chemotherapy on Fetal and Childhood Development

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Cancer is the name given to a collection of diseases characterized by abnormal cell growth that can spread to other parts of the body. Under healthy circumstances, when cells become old or damaged, they die. As a result, new cells are created to take their place. However, as cancer develops, old and damaged cells survive when they are not supposed to and new cells are created when they are not needed, forming tumors (National Cancer Institute, 2015). These tumors can invade surrounding tissue and wreak havoc on the body. Cancer diagnoses during pregnancy are uncommon. It is estimated that only 3,500 cases are diagnosed each year, which correlates to approximately one case per 1,000 pregnancies (0.1%) (Pavlidis, 2002). The management of cancer during pregnancy is complex since it involves both the fetus and the mother. Although there are several treatment options available, they are commonly aggressive and the effectiveness depends on the nature of the patient and their specific diagnosis. The most aggressive treatment, chemotherapy, is often used to kill cancer cells and shrink tumors, however, almost all drugs cross the placenta to the fetus (Leslie, Koil, & Rayburn, 2005). Thus, outcomes after fetal exposure should be examined.

The diagnosis of cancer during pregnancy can create dilemmas for patients and health care providers. Pregnant women may be hesitant to receive cancer treatment due to the potential effects it may have on their developing fetus. According to Doenges, Moorhouse, and Murr (2016), decisional conflict may arise as a result of insufficient information regarding healthcare options, uncertainty about the choices, or if the mother recognizes that there may be undesirable consequences of the treatment being considered. On the other hand, physicians may be hesitant to advise expecting mothers to discontinue

their cancer treatment. Because patient autonomy is one of the most crucial aspects of ethical nursing practice, it is important that pregnant women know the short and long-term risks associated with receiving treatment during pregnancy (Dossey, Keegan, & Barrere, 2016). Examining the effects of chemotherapeutic agents, as well as other treatment alternatives on fetal and childhood development is vital to enhancing maternal autonomy and providing patient-centered care. Well-grounded studies uncovering the short and long-term outcomes of children born to mothers with a cancer diagnosis are limited. The purpose of this thesis is to examine the effects of a maternal chemotherapy on fetal and childhood development. Once identified, these effects will be organized into an educational flier to help nurses better support expecting mothers and enhance their autonomy.

Literature Review

Optimal health does not solely mean the absence of disease, but refers to a state of complete physical, emotional, and social well-being (WHO, 2020). Effectively coping with stress, engaging in fulfilling relationships, and remaining free from disease are all key aspects of a healthful life (CDC, 2020). The first section of this literature review examines the effects of intrauterine chemotherapy exposure on later physical and cognitive development of children. Next, the effects of a parental cancer diagnosis on childhood behavior and mental health are explored. Finally, since breast cancer is commonly diagnosed among women of childbearing age, studies that focus primarily on breast cancer patients and their children are presented.

Physical and Cognitive Development

Chemotherapy targets rapidly growing cells, which is why the rapidly growing fetus becomes a focal point for healthcare providers. Regardless of the type of diagnosis, the

effects of cancer treatment on fetal development is a pronounced concern for women diagnosed with cancer during pregnancy. Before conclusions can be made about the lasting impact of chemotherapeutic agents on fetal development, extensive literature should be explored.

In 2012, Amant, VanCalsteren et al. completed an observational follow-up study to a multicenter cohort study that began in 2005. The follow-up study analyzed 70 children who were prenatally exposed to maternal cancer staging and chemotherapy during the second and third trimesters of pregnancy. Questionnaires regarding general health, school performance, and behavioral and emotional problems were completed by parents. Several neurological tests were performed to determine cognitive development and function of the children. In addition, a detailed cardiac assessment consisting of a 12-lead electrocardiograph (ECG) followed.

Among the 70 children exposed to chemotherapy in utero, 14 had a birth weight below the tenth percentile (20%) (Amant, Van Calsteren et al., 2012). Babies who have a birth weight below the tenth percentile for their gestational age are termed "small for gestational age (SGA)" and may have higher odds of in-hospital death (Finken et al., 2018). In 2011, 15 in every 1,000 term babies were considered SGA (1.5%) (Ewing et al., 2017). In the study by Amant, Van Calsteren et al. (2012), babies exposed to chemotherapy in utero had higher SGA rates than the general population in 2011. However, the incidence and type of congenital malformations were similar to those of the general population and physical examinations and echocardiographic assessments were within normal ranges. Two children (one set of twins) had significant neurocognitive delays and were excluded from further neurodevelopmental testing. Despite this, total IQ scores for the remaining children

were within normal ranges and clinical examinations did not show any neurological abnormalities (Amant, Van Calsteren et al., 2012). Behavior and general health also corresponded with the results of the general population. Overall, fetal exposure to chemotherapy was not specifically associated with poorer long-term outcomes in the children in this study. It was concluded that the long-term outcomes of children in the study were no different than those of the general population.

In 2012, Abdel-Hady et al. compared 61 chemotherapy-exposed children born between 34-35 weeks with 60 non-exposed children born at the same gestational age. Neonatal survival, birth weight, admission to a special care baby unit (SCBU), and congenital malformations were evaluated. Overall, the findings suggested that there were no statistically significant differences in neonatal survival, birth weight, SCBU admissions, or congenital malformations. However, the control group did have better Apgar scores at 1-minute and 5-minutes that were deemed statistically significant – the difference was not significant after 10 minutes (Abdel-Hady, 2012).

Three years later, Cardonick et al. (2015) also investigated the relationship between intrauterine chemotherapy exposure and cognitive ability, school performance, and behavioral competence. In this study, a developmental psychologist performed standardized testing on 35 children who were exposed to chemotherapy in utero and compared the results to those of 22 children who were not exposed. In each of the three areas, no significant differences were determined between the two groups. Across the entire sample, 95% of children scored within the normal ranges on age-appropriate cognitive assessments (Cardonick et al., 2015). When evaluating school performance, mathematics and reading were included. Seventy one percent of all children in the study

demonstrated adequate mathematic ability and 79% demonstrated adequate reading ability (Cardonick et al., 2015). Behaviorally, eight children in the chemotherapy-exposed group displayed behavior problems compared to four children in the non-exposed group (Cardonick et al., 2015). However, these results were not significant. Like Amant et al. (2012), Cardonick et al. (2015) found that no significant differences in cognitive ability, school performance, and behavioral competence were noted in children who were exposed to intrauterine chemotherapy.

The same year, Amant, Vandenbroucke et al. (2015) completed a similar case-control study and compared children whose mothers were diagnosed with cancer and received chemotherapy during pregnancy with children whose mothers were not diagnosed with cancer, and thus, did not receive chemotherapy. All chemotherapy was administered after the first trimester of pregnancy. During the case-control study, health questionnaires and medical files were used to collect data regarding general health. Neurologic examinations and cognitive assessments were also performed. Cognitive functioning was assessed using the Bayley Scales of Infant Development and cardiac function was evaluated according to the American Society of Echocardiography (Amant, Vandenbroucke et al., 2015).

Upon assessment, there were no significant differences in general health and gestational age between the prenatal-exposure group and the control group. Children in the prenatal-exposure group had an average gestational age of 36 weeks and the incidence of medical problems that required surgery were similar between the two groups (Amant, Vandenbroucke et al., 2015). Parental education, as well as sex, race, and country of origin were considered covariates and were taken into consideration when evaluating cognitive

development. Ultimately, results indicated that there were no significant differences in cognitive outcome between children who were exposed to chemotherapy and children who were not exposed. Overall, the cognitive outcomes were similar between groups. However, in all children who were evaluated, there was an average increase of 2.9 points on the Bayley Scales of Infant Development for each week of gestational age (Amant, Vandenbroucke et al., 2015).

After analysis of cardiac function, it was discovered that there were no significant differences in congenital malformations, heart rate, and blood pressure with the chemotherapy-exposed group. Cardiac chamber size and wall thickness were within normal measures, as well as ejection fraction, fractional shortening, longitudinal strain, circumferential strain, and diastolic functioning (Amant, Vandenbroucke et al., 2015). In conclusion, Amant, Vandenbroucke et al. (2015) found that prenatal chemotherapy administered after the first trimester of pregnancy did not have clear adverse effects on cognitive development or cardiac functioning in exposed children.

To further support the idea that chemotherapy does not have significant effects on neonatal development, a systematic review completed by Esposito et al. (2016) explored publications from the last 15 years related to cancer, chemotherapy, pregnancy, and neonatal outcomes. The impact of chemotherapy on embryonic development, along with the perinatal and long-term effects of chemotherapy administered during pregnancy on children were investigated. Because organ formation mainly occurs during the first trimester, the risks associated with the administration of cytotoxic drugs during that time are much more pronounced. According to Gwyn (2005), the use of chemotherapy during the first trimester has the greatest potential for harm to the fetus.

Esposito et al. (2016) found that when chemotherapy is administered in the first trimester, "the risk of malformations is approximately 7% to 17% when a single treatment agent is used and increases to 25% in cases of combination therapy" (p. 2). These malformations may specifically affect the heart, limbs, palate, neural tube, eyes, and ears. However, the long-term impacts of intrauterine chemotherapy were evaluated and showed significantly positive results. Subjects exposed to chemotherapy were followed throughout high school and college and showed normal neurological and psychological development (Esposito et al., 2016). The subjects displayed superior educational performance with no learning disabilities (Esposito et al., 2016). In studies where cardiac functioning was evaluated, there was no evidence of cardiac disease and no structural abnormalities were detected (Esposito et al., 2016). In conclusion, Esposito et al. (2016) found that chemotherapy administered during the first trimester is dangerous, however, when administered during the second and third trimester, the risks of severe problems are low.

Behavior and Mental Health

Problems relating to physical health and cognition are a noticeable concern for expecting mothers, however, a parental cancer diagnosis also has the potential to significantly impact the psychosocial development of children. A cancer diagnosis can place a considerable amount of stress on patients and their families, leading to impaired parenting, less communication, and a lack of consistency in discipline (Faulkner & Davey, 2010). The physical and emotional demands of a cancer diagnosis may also make parents physically and emotionally unavailable, which can cause children to experience psychological stress. Because mental health is a crucial aspect of childhood development, the topic should be explored further.

By interviewing mothers and children who have been affected by a cancer diagnosis, Hoke (2001) aimed to answer the following questions: Are children of mothers with breast cancer more poorly adjusted when compared with children of mothers without breast cancer? Are the medical characteristics of a mother's diagnosis related to the child's outcomes? Do the mother's psychological responses contribute to their child's adjustment? The study compared 28 mothers with breast cancer and their 35 children with 24 mothers with benign biopsies and their 35 children. The Child Depression Inventory, the Revised Children's Manifest Anxiety Scale (RCMAS), The Youth Self-Report, and the Child Behavior Checklist (CBCL) were used to assess affective response, behavior, and social functioning. Both mothers and children participated in completing the assessment tools.

Upon analysis of the reported data, it was revealed that overall functioning did not differ between children of mothers with a breast cancer diagnosis and children of mothers with benign biopsies. Even though mothers with breast cancer reported more personal psychological stress, both groups of children reported fewer anxiety symptoms than the normative sample on the RCMAS scale (Hoke, 2001). Additionally, the Child Behavior Checklist showed that mothers with breast cancer reported fewer behavior problems in their children when compared with the normative sample (Hoke, 2001). Overall, this study did not find evidence that children of breast cancer patients have increased adjustment problems when compared to children of mothers without breast cancer.

Breast Cancer during Pregnancy

Occasionally, breast cancer occurs in women who are pregnant or recently postpartum. According Visco, Meyer, Xi, & Brown (2009), breast cancer occurs approximately once in every 3,000 pregnancies. As the childbearing age in the United

States increases, the prevalence of breast cancer during pregnancy is also likely to increase. Because breast cancer can be diagnosed during a woman's childbearing years, it is important to evaluate the significance of its treatment on pregnant women and their unborn babies.

In 2006, Hahn et al. explained that the prognoses for women diagnosed with breast cancer during pregnancy are similar to those of women without a cancer diagnosis. Even though it has been shown that expecting mothers' outcomes are favorable, concerns for their unborn babies remain. Hahn et al. (2006) followed 57 pregnant women with invasive breast cancer who gave written consent to receive treatment. The identity of each diagnosis determined whether patients were eligible for surgical consultation, neoadjuvant chemotherapy, or systemic chemotherapy (FAC). When evaluating the children who were exposed to systemic chemotherapy in utero, gestational age at the beginning of treatment, the number of cycles of FAC, and total dosages were recorded. To determine outcomes, "neonatal complications, and subsequent health, development, and educational performances" were obtained via parent and guardian surveys (Hahn et al., 2006, p. 1221). At the time of the study, the children's ages ranged from 2 to 157 months. In most cases, chemotherapy was not initiated until the second trimester.

First and foremost, there were no stillbirths, miscarriages, or perinatal deaths among children who were subjected to FAC chemotherapy in utero. Additionally, most of the children did not have significant neonatal complications and primarily resembled the general population (Hahn et al. 2006). When looking at school age children, only two required special attention at school, one had attention deficit disorder, and one was diagnosed with Down Syndrome (Hahn et al., 2006). All children, besides the child with

Down Syndrome, were said to have normal development when compared with other children at similar ages. Despite exposure to chemotherapy, all parents who responded to the survey felt that their child was healthy. Another study conducted by Murthy et al. (2014) presented similar findings.

Between 1992 and 2010, 81 pregnant women participated in an institutional review board (IRB)-approved trial, in which they received a "standardized chemotherapy regimen during the second and third trimesters of their pregnancy" and provided follow-up information about their children (Murthy et al., 2014, p. 2). Prior to delivery, the patients received combination chemotherapy. Each participant gave consent for their delivery records to be obtained and health questionnaires were administered to collect data regarding their child's current health status and developmental/social history.

Out of the 81 participants, 63 participants or their next of kin answered the questionnaire. Overall, 81 children were born after exposure to chemotherapy in utero at a mean gestational age of 37 weeks and a mean birth weight of 2.9 kg (Murthy et al., 2014). Twenty-eight of the children were delivered preterm, however, only two were delivered before gestational week 33 and most of the preterm births were spontaneous without complications. When evaluating neonatal complications among the sample, the following complications were noted: required supplemental oxygen at the time of delivery (11), had subarachnoid hemorrhage (1), had hypoglycemia (2), and had jaundice (3) (Murthy et al., 2014). Of the children who had neonatal complications, 62% were exposed to more than four cycles of chemotherapy in utero. Post-neonatal outcomes resembled the outcomes presented in the study done by Hahn et al. (2006). Parents who responded to the survey considered their children to be healthy overall. Twelve-percent of the survey responders

reported developmental milestone delays, which included language delays (Murthy et al., 2014). However, there were no significant cognitive abnormalities reported. Overall, "the rate of congenital abnormalities in [the study's] population [was] similar to the US average rate" (Murthy et al., 2014, p. 5). Overall, it was found that combination chemotherapy administered to patients during pregnancy does not impose significant health risks to fetal development and the children in the study did not "indicate a higher rate of serious medical problems than seen in the general population" (Murthy et al., 2014, p. 6).

The results of the breast cancer patients and their children were similar to the results of patients with different types of cancer. However, it is important look at breast cancer specifically since it is the most common form of cancer diagnosed during pregnancy (Esposito et al., 2016).

Limitations

The goal of this literature review was to explore the effects of maternal chemotherapy on fetal and childhood development and provide evidence to expecting mothers to enhance their autonomy when determining courses of treatment. However, limitations do exist within the review. One limitation is the age of the articles. Out of the 16 articles, most of them were written in the early 2000s and only five were written within the last five years. The systematic review, written in 2016, is one of the most recent articles. This indicates that the number of studies that explore the topic of maternal chemotherapy on fetal and childhood development have decreased. It can be presumed that the discontinuation of research was due to repetitive findings since the results of earlier studies are comparable to the results of recent studies. This may show that throughout time, the effects of maternal chemotherapy on fetal and childhood development has

remained unchanged and does not pose significant risks. Sample size is another limitation of this literature review. Many of the sample sizes in the studies were small. A small sample size may reduce the power of the study and increase the margin of error.

When analyzing these findings, the presence of the blood-brain barrier should be taken into consideration. According to Deeken and Löscher (2007), "the blood-brain barrier is a physiologic obstruction to the delivery of systemic chemotherapy to the brain parenchyma and central nervous system" (p. 1663). The reason there are limited cognitive and developmental effects of chemotherapy on the developing fetus in these studies may be due to the protective blood-brain barrier.

Implications for Practice and Conclusion

Pregnant patients who have been diagnosed with cancer have the right to decide whether they will receive treatment during pregnancy or not. However, health-related decisions should not be taken lightly, especially when the decisions can affect a mother and her unborn baby. Expecting mothers may experience fear related to their diagnosis, which can result in decisional conflict and impaired decision making. Thus, it is important to determine the patient's perception of the problem, actively listen to the patient's concerns, correct misperceptions the patient may have, and provide factual information (Doenges et al., 2016). Helping the patient identify internal and external resources for assistance and support may also enhance the client's sense of optimism (Doenges et al., 2016).

Nurses and other health care providers have the knowledge and ability to encourage patients to make well-informed decisions. Therefore, providing accurate data about the short and long term effects of chemotherapy on fetal and childhood development is essential. After exploring several studies, it has been repeatedly shown that maternal

chemotherapy given after the first trimester of pregnancy does not appear to have a significant impact on the physical or cognitive development of fetuses or children. Maintaining open and transparent lines of communication gives health care providers the opportunity to reassure patients that cancer treatment given after the first trimester is safe for their unborn baby.

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The Nursing Crier

Effects of Maternal Chemotherapy on Fetal and Childhood Development

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Scope and Impact of the Problem

It is estimated that nearly 3,500 women are diagnosed with cancer during pregnancy each year[1,9]. Although there are several treatment options available, they can be aggressive. Pregnant women may be hesitant to receive cancer treatment due to the potential effects it can have on their developing fetus. On the other hand, physicians may be hesitant to advise expecting mothers to discontinue their cancer treatment. Because patient autonomy is one of the most crucial aspects of ethical nursing practice, it is important that pregnant women know the short and long-term risks associated with receiving chemotherapy during pregnancy. Evaluating pediatric outcomes after chemotherapy exposure and providing expecting mothers with evidence-based information are vital to enhancing patient autonomy and providing quality patient care.

Expected Nursing Practice

Expecting mothers with a cancer diagnosis should be provided evidence-based information regarding the effects of cancer treatment on fetal and childhood development to support their decision to either undergo treatment during pregnancy or withdraw.

Supporting Evidence

Patient-centered care and patient autonomy are two of the most noteworthy aspects of nursing practice. Allowing patients the opportunity to analyze the short and long-term effects of chemotherapy exposure will provide them with a sense of control when deciding to proceed with treatment or withdraw.

It is understandable that expecting mothers may be hesitant to undergo treatment without proper knowledge about its impact. However, it is also understandable that health care providers may be hesitant to guide patients to discontinue treatment. One of the main goals of quality health care is to provide the largest benefit to the greatest number of individuals. By providing adequate information, health care providers can improve patient outcomes.

Studies have shown the following findings regarding the effects of a maternal cancer diagnosis and chemotherapy on fetal and childhood development:

1. There are no significant differences in cognitive ability when comparing children who were exposed to chemotherapy in utero with children who were not exposed[6]. Chemotherapy is not associated with poorer neurodevelopmental outcomes in children[1,2,3,5,8]. Children exposed to chemotherapy scored within normal ranges on age-appropriate cognitive assessments[2].

2. Congenital malformations, heart rate, and blood pressure are similar between chemotherapy-exposed children and children who were not exposed[3,7,8]. Electrocardiograph assessments and physical evaluations do not show significant abnormalities in chemotherapy-exposed chilren[1,3]. Overall cardiac functioning is not impaired from exposure to chemotherapy[1,3,8].

3. No differences are noted in behavioral competence between groups[1,2,5]. Parents also report fewer behavior problems in chemotherapy-exposed children[4].

4. Anxiety symptoms in chemotherapy-exposed children are similar to those of non-exposed children[4].

5. Exposed children who were followed throughout high school and college showed normal neurological and psychological development[8]. The chemotherapy-exposed children displayed superior educational performance with no learning disabilities[8].

6. Parents of children who have been exposed to chemotherapy report that their children maintain optimal levels of overall health[5,6]. Overall, parent perceptions of child wellness are positive.

Actions for Nursing Practice

Determine the patient's perception of what is occurring and how this will affect life. *How the client views the situation determines how they will react*[10].

Actively listen to the client's concerns. *Listening conveys a message of belief and confidence in the client*[10].

Assist client in learning how to find factual information. *Knowledge gained will allow the client to make well-informed decisions*[10].

Support involvement of family/significant others as desired/appropriate. *This will provide the client with a local support system and enhance familial relationships*[10].

Identify internal and external resources for assistance. *Helping the patient identify available resources increases the likelihood that they will be used in the future*[10].

Encourage contact with another individual who has successfully dealt with a similar fearful situation. *This may enhance the client's sense of optimism*[10].

Need More Information or Help?

1. The National Cancer Institute offers extensive up-to-date cancer information from the United States government's principle agency for cancer research. This resource is available at https://www.cancer.gov.

2. The National Foundation for Cancer Research provides information regarding research programs, tips to prevent and fight cancer, and offers outlets to donate to cancer research. To learn more, go to https://www.nfcr.org.

3. The Society for Maternal-Fetal Medicine offers practice and career support, clinical guidance, in-person and online educational opportunities, patient safety recommendations, and other supplemental documents to members. This resource can be found at https://www.smfm.org.

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Hierarchy of Evidence for Intervention Studies

Type of evidence	Level of evidence	Description
Systematic review or meta-analysis	I	A synthesis of evidence from all relevant randomized controlled trials.
Randomized controlled trial	II	An experiment in which subjects are randomized to a treatment group or control group.
Controlled trial without randomization	III	An experiment in which subjects are nonrandomly assigned to a treatment group or control group.
Case-control or cohort study	IV	Case-control study: a comparison of subjects with a condition (case) with those who don't have the condition (control) to determine characteristics that might predict the condition. Cohort study: an observation of a group(s) (cohort[s]) to determine the development of an outcome(s) such as a disease.
Systematic review of qualitative or descriptive studies	V	A synthesis of evidence from qualitative or descriptive studies to answer a clinical question.
Qualitative or descriptive study	VI	Qualitative study: gathers data on human behavior to understand *why* and *how* decisions are made. Descriptive study: provides background information on the *what*, *where*, and *when* of a topic of interest.
Expert opinion or consensus	VII	Authoritative opinion of expert committee.

Adapted with permission from Melnyk BM, Fineout-Overholt E, editors. Evidence-based practice in nursing and healthcare: a guide to best practice [forthcoming]. 2nd ed. Philadelphia: Wolters Kluwer Health/Lippincott Williams and Wilkins.

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