ISFP – Newsletter

The need for preconception care regarding perinatal complications for cancer survivors

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Since the publication of the 2006 guidelines of the American Society of Clinical Oncology (ASCO),[1)] chemotherapy and radiotherapy are widely known to have an impact on gonadal function. To preserve fertility in young cancer patients, cryopreservation of sperm, oocytes, embryos, and ovarian tissues is conducted in many countries across the world, and a 2017 review reported 120 live childbirths after transplantation of cryopreserved and thawed ovarian tissues.[2)] In the meantime, this fertility preservation technology has become part of routine clinical practice in some countries. However, cancer treatment causes a wide variety of complications; well-known complications include neurological conditions[3)] (such as posterior cavity syndrome, secondary neoplasms, cognitive function disturbance, and cerebellar dysfunction) and cerebrovascular disorders.[4)] Furthermore, an increased incidence of perinatal complications has been sporadically reported in female cancer survivors who became pregnant. The 5-year survival rate of pediatric cancer patients has now increased to as high as 80%,[5),6)] and long-term survival is common in many young cancer patients. Therefore, perinatal risks for pregnant cancer survivors should be considered and are the topic of the present newsletter.

Preterm delivery

Some researchers reported that female CAYA (childhood, adolescent, and young adult) cancer survivors have a higher risk of preterm delivery than their sisters or women in the general population.[7)] Melin and colleagues assessed 1800 female cancer survivors in Finland and found that the incidence of preterm delivery was 8.0% in this population and 5.3% in the sibling population.[8)] Mueller and colleagues evaluated 892 women with live births who were diagnosed with cancer when younger than 20 years and reported that chemotherapy plus radiation therapy doubled the risk of preterm delivery concerning chemotherapy alone (chemotherapy alone, 1.99-fold increase; chemotherapy plus radiation therapy, 2.22-fold increase).[9)] Recently, van de Loo and colleagues assessed 55 women who underwent irradiation of the abdominal region for cancer treatment at an age of 18 years or younger and survived for at least 5 years, and they found that the incidence of preterm delivery was 10.31 times higher in this population than in the general population.[10)] Signorello and colleagues assessed 1264 female cancer survivors and reported that the incidence of preterm delivery was higher in the group who underwent high-dose radiation therapy (> 5 GY) than in the group not treated with radiation therapy (50.0% vs 19.6%, respectively).[11)] They also reported that the incidence of preterm delivery tended to increase from a low dose of 0.5 Gy.
To sum up, both chemotherapy and radiotherapy have been suggested to raise the risk of preterm delivery.

Low birth weight newborns

The prevalence of low birth weight babies, i.e., babies that weigh less than 2500 g, has been reported to be higher in CAYA cancer survivors.[7)] Mueller and colleagues found that the incidence of delivery of low birth-weight babies was 1.31 times higher in female CAYA cancer survivors than in women in the general population. Signorello and colleagues reported that the incidence of delivery of low birth weight babies was 9.0% in cancer survivors and 4.2% in their siblings.[11)] They found no significant difference between the two groups, but when the incidence was adjusted for the mother's age, order of birth, child sex, mother's alcohol consumption, mother's smoking habit, and use of assisted

reproductive technology, the incidence of delivery of low birth-weight babies doubled in the cancer survivors and the difference became statistically significant. About the impact of radiation in the abdominal region, van de Loo and colleagues assessed 55 women who underwent such radiation for cancer treatment at age 18 years or younger and 220 control cancer survivors (without radiotherapy) and reported that the incidence of low birth weight babies was 6.86 times higher in the former group.[10] In addition, a radiation dose-dependent impact was noted in the survivors treated with radiation for Wilms' tumor.[12] Furthermore, a correlation was reported between the incidence of low birth weight babies and radiation dose in female survivors treated with radiation of the uterus at doses greater than or equal to 2.5 Gy[11] and those treated with radiation of the pelvis at doses greater than or equal to 25 Gy.[13]

Gestational hypertension syndrome

The reported impacts of radiation in the abdominal region include hypertension syndrome during pregnancy. Reulen and colleagues assessed 2783 cases of single embryo gestation in 1712 female survivors of pediatric cancer and reported that the incidence of hypertension during pregnancy was 3.29-fold higher in the survivors of Wilms' tumor treated with radiation in the abdominal region (n = 127) than in those not treated with radiotherapy.[14] However, these figures are for Wilms' tumor, which is a rare disease. Furthermore, other researchers did not find an increased risk of hypertension during pregnancy, although they assessed 6[15] and 19[16] patients who had undergone radiation of the abdominal region. Therefore, the difference in the study results may be attributable to the different sample sizes.

Gestational diabetes

To investigate the incidence of diabetes during pregnancy, Hagger and colleagues compared 1,894 female survivors of adolescent and young adult (AYA) cancer with women without a history of cancer.[17] They found that the incidence of gestational diabetes was 1.38-fold higher in the female survivors of AYA cancer than in the control women (5% vs 2%, respectively). Furthermore, this tendency of cancer survivors to develop gestational diabetes became more pronounced with age.[17] Reulen and colleagues reported that the incidence of gestational diabetes was 3.35-fold higher in cancer survivors treated with radiation in the abdominal region than in cancer survivors not treated with radiotherapy.[14] The increased incidence of gestational diabetes was observed in both survivors of Wilms' tumor (2.73 times higher) and survivors without Wilms' tumor (4.27 times higher). Overall, gestational diabetes affected 4.9% of survivors treated with abdominal radiation, 1.5% of survivors not treated with radiotherapy, and 1.6% of women in the general population.

Gestational anemia

Reulen and colleagues reported that the incidence of anemia during pregnancy was 2.1 times higher in cancer survivors treated with abdominal radiation than in survivors not treated with radiotherapy.[14] They also found that the incidence of anemia during pregnancy increased in both survivors of Wilms' tumor (2.00 times higher) and survivors of other types of cancer (2.25 times higher). However, Mueller and colleagues reported that the incidence of maternal anemia in cancer survivors was similar to that in women in the general population.[18] However, their study cohort was not limited to cancer survivors treated with radiation.

Taken together, the research does not suggest that the risk of maternal anemia is higher in general cancer survivors.

Child deformities

Many reports state that the risk of birth defects in newborns is not higher in offspring of cancer survivors.[7]

Cesarean section

Reulen and colleagues reported that the frequency of elective Caesarean section was 1.39 times higher in cancer survivors not treated with radiotherapy than in the general population.[14] In particular, the frequency was 1.52 times higher in survivors of bone tumors and 1.46 times higher in survivors treated with radiation in the abdominal region. However, the frequency of emergency Caesarean section was not higher in cancer survivors than in the general population.

Etiology

To date, many reports have described the impacts of cancer treatment, including late complications related to the radiation of the abdomen. The increased incidences of preterm delivery and low birth weight offspring represent radiation-related late complications. The mechanism of such complications is not completely understood; however, vascular scarring, atrophy, and sclerosis have been suggested as possible causes. If a radioactive ray is irradiated directly onto the uterine, it causes histological changes, such as atrophic fascia, pronounced fibrosis in the inner half layer (submucosal layer), and edematous serosal surface. The irradiated myometrium becomes atrophic and thinner, with diminished blood vessels.[19] Thus, radioactive irradiation is likely to reduce reproductive capacity by damaging the uterine fascia, endometrium, and uterine vascular system. Radiation-induced fibrosis is one example of a histological change due to radiation and is characterized mainly by non-specific changes of the connective tissues, excessive deposition of extracellular matrix, excessive proliferation of myofibroblasts, and the presence of inflammatory infiltrate.[19] The uterine volume was reported to be significantly smaller in cancer survivors who underwent radiation of the abdominal region during childhood than in cancer survivors treated with chemotherapy alone.[20] Thus, radiotherapy during childhood is suggested to have a long-term impact on the uterus. In general, direct high-dose radiation (> 25 Gy) in children causes irreversible damage to the uterine vascular system and muscular function.[20] Therefore, even though uterine volume can be temporarily increased by hormonal therapy, radiation-related perinatal risks should be strictly monitored.

In recent years, fertility preservation has been widely conducted across the world. However, radiotherapy can have a long-term impact on the uterus. Therefore, during perinatal healthcare of cancer survivors due to attention should be paid to the risk of radiotherapy. Because increased risks of preterm delivery and low birth-weight offspring have been noted in cancer survivors, it is recommended that medical management of pregnancy be implemented at high-level medical institutions.

References

1) Lee, S. J., et al. (2006). "American Society of Clinical Oncology recommendations on fertility preservation in cancer patients." J Clin Oncol 24(18): 2917-2931.
2) Donnez, J. and M. M. Dolmans (2017). "Fertility Preservation in Women." N Engl J Med 377(17): 1657-1665.
3) Sun, L. R. and S. Cooper (2018). “Neurological Complications of the Treatment of Pediatric Neoplastic Disorders.” Pediatr Neurol 85: 33-42.
4) Scholz-Kreisel, P., et al. (2017). “Prevalence of cardiovascular late sequelae in long-term survivors of childhood cancer: A systematic review and meta-analysis.” Pediatr Blood Cancer 64(7).
5) Phillips, S. M., et al. (2015). "Survivors of childhood cancer in the United States: prevalence and burden of morbidity." Cancer Epidemiol Biomarkers Prev 24(4): 653-663.
6) Martinez, F., and E.-A. E. W. G. International Society for Fertility Preservation (2017). "Update on fertility preservation from the Barcelona International Society for Fertility Preservation-ESHRE-ASRM 2015 expert meeting: indications, results and future perspectives." Fertil Steril 108(3): 407-415 e411.
7) van der Kooi, A. L. F., et al. (2021). "Counseling and surveillance of obstetrical risks for female childhood, adolescent, and young adult cancer survivors: recommendations from the International Late Effects of Childhood Cancer Guideline Harmonization Group." Am J Obstet Gynecol 224(1): 3-15
8) Melin, J., et al. (2015). "Adverse Obstetric Outcomes Among Early-Onset Cancer Survivors in Finland." Obstet Gynecol 126(4): 803-810.

9) Mueller, B. A., et al. (2009). "Pregnancy outcomes in female childhood and adolescent cancer survivors: a linked cancer-birth registry analysis." Arch Pediatr Adolesc Med 163(10): 879-886.
10) van de Loo, L., et al. (2019). "Uterine function, pregnancy complications, and pregnancy outcomes among female childhood cancer survivors." Fertil Steril 111(2): 372-380.
11) Signorello, L. B., et al. (2006). "Female survivors of childhood cancer: preterm birth and low birth weight among their children." J Natl Cancer Inst 98(20): 1453-1461.
12) Green, D. M., et al. (2002). "Pregnancy outcome after treatment for Wilms tumor: a report from the National Wilms Tumor Study Group." J Clin Oncol 20(10): 2506-2513.
13) Chiarelli, A. M., et al. (2000). "Pregnancy outcomes in females after treatment for childhood cancer." Epidemiology 11(2): 161-166.
14) Reulen, R. C., et al. (2017). "Pregnancy and Labor Complications in Female Survivors of Childhood Cancer: The British Childhood Cancer Survivor Study." J Natl Cancer Inst 109(11).
15) Lie Fong, S., et al. (2010). "Pregnancy outcome in female childhood cancer survivors." Hum Reprod 25(5): 1206-1212.
16) Sekiguchi, M., et al. (2018). "Pregnancy outcomes in female childhood cancer survivors: Nationwide survey in Japan." Pediatr Int 60(3): 254-258.
17) Haggar, F. A., et al. (2014). "Adverse obstetric and perinatal outcomes following treatment of adolescent and young adult cancer: a population-based cohort study." PLoS One 9(12): e113292.
18) Mueller, B. A., et al. (2009). "Pregnancy outcomes in female childhood and adolescent cancer survivors: a linked cancer-birth registry analysis." Arch Pediatr Adolesc Med 163(10): 879-886.
19) Arrive, L., et al. (1989). "Radiation-induced uterine changes: MR imaging." Radiology 170(1 Pt 1): 55-58.
20) Larsen, E. C., et al. (2004). "Radiotherapy at a young age reduces the uterine volume of childhood cancer survivors." Acta Obstet Gynecol Scand 83(1): 96-102.