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Updates in preserving reproductive potential of prepubertal girls with cancer: Systematic review

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ABSTRACT

Introduction: With increasing numbers of adult female survivors of childhood cancers due to advances in early diagnosis and treatment, the issue of preserving the reproductive potential of prepubertal girls undergoing gonadotoxic treatments has gained greater attention.
Methods: According to PRISMA guidelines, a systematic review of the literature was performed for all relevant full-text articles published in PubMed in English throughout the past 15 years to explore the significant updates in preserving the reproductive potential of prepubertal girls with cancer.
Results: The two established fertility preservation options, embryo freezing and egg freezing, cannot be offered routinely to prepubertal girls as these options necessitate prior ovarian stimulation and subsequent mature oocytes retrieval that are contraindicated or infeasible before puberty. Therefore, the most suitable fertility preservation options to prepubertal girls are (1) ovarian tissue freezing and autotransplantation, (2) in vitro maturation, and (3) ovarian protection techniques. In this review, we discuss in detail those options as well as their success rates, advantages, disadvantages and future directions. We also suggest a new integrated strategy to preserve the reproductive potential of prepubertal girls with cancer.

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Conclusion: Although experimental, ovarian tissue slow freezing and orthotopic autotransplantation may be the most feasible option to preserve the reproductive potential of prepubertal girls with cancer. However, this technique has two major and serious disadvantages: (1) the risk of reintroducing malignant cells, and (2) the relatively short lifespan of ovarian tissue transplants. Several medical and ethical considerations should be taken into account before applying this technique to prepubertal girls with cancer.

1. Introduction

Puberty in girls refers to the physiological process of sequential endocrine, physical and psychological changes leading to the development of sexual and reproductive functions. Although unclear, the onset of puberty in girls is likely related to complete activation of hypothalamic-pituitary-ovarian (HPO) axis. With some variability observed depending on several genetic, environmental and nutritional factors, puberty in girls starts usually at the age of 9–11 and is completed at the age of 15–17. The most important sign of puberty in girls is menarche, the first menstrual cycle, which occurs usually at the age of 12 due to commencement of both endocrine and reproductive ovarian functions (Fritz and Speroff, 2011a; Biro et al., 2012; Colvin and Abdullatif, 2013). By definition, prepubertal girls are the girls who have not started or completed puberty (age 0–15) (Resetkova et al., 2013). Biologically, prepubertal girls have great reproductive potential due to the great number of oocytes in their ovaries. The peak number of oocytes is about 7 million during mid-intrauterine life, then it declines to approximately 2 million at birth, and almost half a million at puberty (Fritz and Speroff, 2011b). However, when a prepubertal girl gets exposed to aggressive chemotherapy and radiotherapy for cancer treatment, gonadotoxicity occurs as a side effect which may lead to severe ovarian damage, complete depletion of oocytes and permanent loss of reproductive potential (Wallace et al., 2005; Sauvat et al., 2009; Jadoul et al., 2010; Wallace, 2011; Dillon and Gracia, 2012).

With increasing numbers of adult female survivors of childhood cancers due to advances in early diagnosis and treatment, the issue of preserving the reproductive potential of prepubertal girls undergoing gonadotoxic treatments has gained greater attention (Wallace et al., 2005; Sauvat et al., 2009; Jadoul et al., 2010; Wallace, 2011; Dillon and Gracia, 2012). In this review, we investigate in detail the possible options for preserving the reproductive potential of prepubertal girls with cancer and we also address the significant updates in this field.

2. Methods

According to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Liberati et al., 2009), a systematic review of the literature was performed for all relevant full-text articles published in PubMed in English throughout the past 15 years to explore the significant updates in preserving the reproductive potential of prepubertal girls with cancer. Based on these inclusion criteria, the following electronic search strategy was performed in PubMed: (((((fertility preservation) AND girls) AND cancer) OR oncofertility) AND full text[sb] AND ("2000/01/01"[PDat]: "2015/09/30"[PDat]) AND English[lang]). The full-text articles identified from the initial search underwent screening for titles and abstracts and were then checked for eligibility according to the inclusion criteria. Only the full-text articles that focus completely or partially on preserving the reproductive potential of prepubertal girls with cancer were included and fully reviewed. Data was extracted from the text, tables, graphs and references of the included articles.

3. Results

A total of 171 full-text articles were identified from the initial search ~88% of them were published in the past 5 years, confirming the growing attention towards the topic. After screening titles and abstracts, all 171 full-text articles were checked for eligibility according to the inclusion criteria. Only nine full-text articles were excluded while the remaining 162 full-text articles that focused completely or partially on preserving the reproductive potential of prepubertal girls with cancer were included and fully reviewed. PRISMA Flow Diagram of the systematic review process is illustrated in Fig. 1. Some significant articles were not identified from the initial search but we fully reviewed them as well. Therefore, the final reference list was generated on the basis of originality and relevance to the broad scope of this review.

3.1. Epidemiology of cancer in prepubertal girls

According to recent reports, approximately 82,000 prepubertal girls are diagnosed with cancer each year worldwide. The most common cancers in prepubertal girls in most parts of the world are leukemia, central nervous system malignancies and lymphoma respectively (American Cancer Society, 2015). According to the American Cancer Society in 2014, it is estimated that the number of prepubertal girls diagnosed annually with cancer in the USA is approximately five thousand, with an increasing overall five-year survival rate (82%) due to advances in early diagnosis and treatment. The most common cancers in prepubertal girls in the USA are leukemia (31%), central nervous system malignancies (21%), and lymphoma (10%) (Ward et al., 2014). According to the German Childhood Cancer Registry in 2014, it is estimated that the number of prepubertal girls diagnosed annually with cancer in Germany is approximately one thousand, with an increasing overall five-year survival rate (81%) due to advances in early diagnosis and treatment. The most common cancers in prepubertal girls in Germany are leukemia (30.9%), central nervous system malignancies (23.7%), and lymphoma (14.1%) (German Childhood Cancer Registry (GCCR), 2014).

3.2. Side effects of chemotherapy and radiotherapy in prepubertal girls

In prepubertal girls, chemotherapy and radiotherapy can lead to gonadotoxicity, ovarian damage, oocyte depletion and subsequent risk of reproductive potential loss which is related mainly to (1) the type, dose and dosage of chemotherapy and radiotherapy used, and (2) the age of the girl at the beginning of treatment. Chemotherapy is the first-line of treatment for most of childhood cancers. Alkylating agents such as cyclophosphamide, ifosfamide, and procarbazine are the most gonadotoxic regimens to the ovary. Radiotherapy may be also used alone or in a combination with chemotherapy for treatment of some childhood cancers. Pelvic, abdominal and total body irradiation are the most gonadotoxic radiotherapies to the ovary with effective total sterilization doses 20.3 Gy at birth, 18.4 Gy at