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Fertility and hormone preservation and restoration for female children and adolescents receiving gonadotoxic cancer treatments: A systematic review☆

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ABSTRACT

Background/Purpose: The purpose of this systematic review by the American Pediatric Surgical Cancer Committee was to summarize evidence from the current medical literature regarding fertility restoration and hormone replacement for female children and adolescents treated with gonadotoxic treatments.
Methods: Using PRISMA guidelines, questions were addressed by searching Medline, Cochrane, Embase Central and National clearing house databases using relevant search terms. Eligible studies included those that addressed ovarian tissue cryopreservation (OTC), oocyte harvest, ovarian transposition, and ovarian tissue auto-transplantation for females under the age of 20. Four reviewers independently screened studies for eligibility, extracted data and assessed the risk of bias. Study outcomes were summarized in a narrative synthesis.
Results: Two thousand two hundred seventy-six studies were identified by database search and manual review and 2185 were eliminated based on defined exclusion criteria. Ninety-one studies served as the basis for the systematic review. There were 1019 patients who underwent OTC with ages ranging from 0.4 to 20.4 years old, with 298 under the age of 13. Twenty patients aged 13–20 years old underwent successful oocyte harvest. Thirty-seven children underwent ovarian transposition as a means of fertility preservation. Eighteen patients underwent auto-transplantation of thawed ovarian cortical tissue that was harvested before the age of 21 years resulting in 10 live births.
Conclusions: Clinically accepted and experimental fertility preservation options such as OTC, oocyte cryopreservation, and ovarian transposition are available to females aged 20 years and younger who are at risk for premature ovarian insufficiency and infertility due to gonadotoxic treatments. There is a large cohort of pediatric-aged patients, with a wide variety of diagnoses and treatments, who have undergone fertility preservation. Currently, fertility and hormone restoration experience for patients who were 20- years of age or younger at the time of fertility preservation remains limited.
Level of Evidence: IV.

Abbreviations: OTC, ovarian tissue cryopreservation; IVF, *in vitro* fertilization; IVM, *in vitro* maturation; PRISMA-P, Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols; ASRM, American Society of Reproductive Medicine; MI, Metaphase I; MII, Metaphase II.

☆ For the Cancer Committee of the American Pediatric Surgical Association.

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The rates of survivorship for children and adolescents diagnosed with cancer have improved significantly over the past four decades. Focus has now shifted towards ensuring a better quality of life for survivors. Currently, children who receive a new cancer diagnosis can expect upwards of an 80% five-year survival rate with the majority of patients living into adulthood [1]. Survivors of childhood cancer have reported future fertility and the ability to have biological children as a quality of life priority [2,3]. Reduced fertility and premature gonadal insufficiency can be directly related to removing the gonad, or as the result of high-intensity, multi-modality treatments such as alkylating chemotherapy agents (eg, cyclophosphamide, busulfan), radiation therapy (pelvic, whole abdomen, cranial, total body), and stem cell transplantation that are utilized to treat many pediatric malignancies [4–6].

The American Academy of Pediatrics, American Society of Clinical Oncology, and the American Society of Reproductive Medicine (ASRM) recommend that clinicians discuss the consequences of planned medical treatments on future fertility, the possibility of premature gonadal insufficiency, and available fertility preservations options with patients and their families [7–9]. Despite these recommendations, very few patients receive adequate fertility preservation counseling [3]. Barriers to oncofertility discussions may include underappreciation of the importance of fertility preservation to patients and their families, as well as a lack of knowledge, minimal experience, and/or clinician discomfort with the topic [10,11].

At this time, there are both clinically accepted and experimental methods for fertility preservation for girls, depending on pubertal status, who are expected to receive gonadotoxic radiation and chemotherapy [9,12]. The purpose of this systematic review is to report the use and distribution of fertility preservation procedures, including ovarian tissue cryopreservation (OTC), oocyte cryopreservation, and ovarian transposition for pediatric-aged patients and highlight fertility and hormone restoration outcomes.

1. Methods

1.1. Search strategy

This systematic review was written in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) guidelines and statement. We searched MEDLINE (Ovid), Embase (Elsevier), Web of Science (Thomson Reuters), and Cochrane Library (Wiley) databases from the date of inception to February 2018. We identified text words and controlled vocabulary terms for the following concepts: adolescent and young adult females, potential sterilizing medical treatments including, fertility preservation procedures, and fertility restoration techniques. We applied database-specific logic and wildcards. There were no restrictions to publication date, document type, or language. The searches were supplemented with a manual review of references from included articles and studies identified from hand searching. Study authors were contacted from those institutions with multiple publications and possible overlapping study cohorts and results were updated accordingly.

1.2. Study selection

Inclusion criteria were human studies that focused on fertility preservation methods for children, adolescents, and young adults 20 years old or younger who received gonadotoxic treatment for their cancer or medical condition. Excluded studies were those focused on patients greater than 21-years-old. All papers that were identified in the search strategy were exported into Rayyan for de-duplication and uploaded for screening [13]. Four members of the study team (KSC, DSR, MBM, TBL) manually reviewed record titles and abstract and excluded studies based on the aforementioned criteria. Two members reviewed the first half of the abstracts (KSC, TBL), while the other two members reviewed the second half of resulted abstracts (DSR, MBM). If consensus was not reached by both reviewers, two members of the study team (KSC, TBL) reviewed conflicted abstracts. Included abstracts were then subjected to full-text review by three study members (KSC, TBL, DSR). If consensus was not reached, a fourth reviewer (MBM) was included.

1.3. Data extraction and analysis

Study characteristics were extracted from each publication and included study type and level of evidence, number of patients, ages, pubertal status, OTC cases (surgical technique, in vitro maturation, complications), oocyte harvest (stimulation type, number of oocytes harvested, complications), and ovarian transposition (complications). In addition, details regarding auto-transplantation (age at transplant, location, hormone restoration, pregnancy, live birth, method, complications) were collected. Relevant findings were extracted by one member (KSC) and verified by two members (TBL, DSR) of the research team.

2. Results

2.1. Search outcomes

The initial database searches identified 2262 published articles. Our manual review of references identified an additional 14 non-duplicate studies for abstract evaluation. Of these 2276 studies, we eliminated 2114 during abstract review and an additional 71 after full-text review based on the defined exclusion criteria described earlier. The remaining 91 studies serve as the basis for the systematic review. The selection process, based on the PRISMA-P schema, is detailed in Fig. 1.

2.2. Study characteristics

Ninety-one studies were included in the review, of which 53 discuss fertility preservation methods (ovarian tissue or oocyte cryopreservation, ovarian transposition), 17 discuss fertility and hormone restoration (auto-transplantation of ovarian tissue), and 21 discuss both. The majority were retrospective cohort studies. The included studies representing 21 countries, with 11 reported from European institutions.

2.3. Fertility preservation procedures

Seventy-four studies were identified that addressed fertility preservation methods such as OTC, oocyte cryopreservation, oophoropexy, and/or transposition of the ovary. Of these reports, 46 provided specific data on fertility preservation for patients who were 20 years old or younger at the time of OTC. The remainder of the studies were mixed population studies, institutional duplicates, or review articles.

2.3.1. Ovarian tissue cryopreservation

Thirty-five studies had extractable data for children under the age of 20 who underwent OTC. After removing institutional duplicates, 23 representative studies remained. Personal communication to authors at high-volume institutions was carried out. Two institutions provided up-to-date OTC participation numbers. (Table 1) There were 1019 patients represented with ages ranging from 0.4 to 20.4 years old, with 298 under the age of 13. Of the 20 studies that included operative details within their methods or results, 57.0% (415/728) of patients underwent an oophorectomy and 43.0% (313/728) had a partial oophorectomy or ovarian biopsies. Oocyte aspiration of antral follicles and/or filtration of washings at the time of tissue processing occurred for 71 cases [14–19]. A slow-freeze cryopreservation protocol of ovarian cortical strips was described by all institutions that reported their cryopreservation techniques. A large multi-center cohort publication noted minor bleeding as a complication after surgery [20]. Lima et al noted one episode of perioperative bleeding requiring transfusion and Chambon et al report one instance of post-operative bleeding requiring re-

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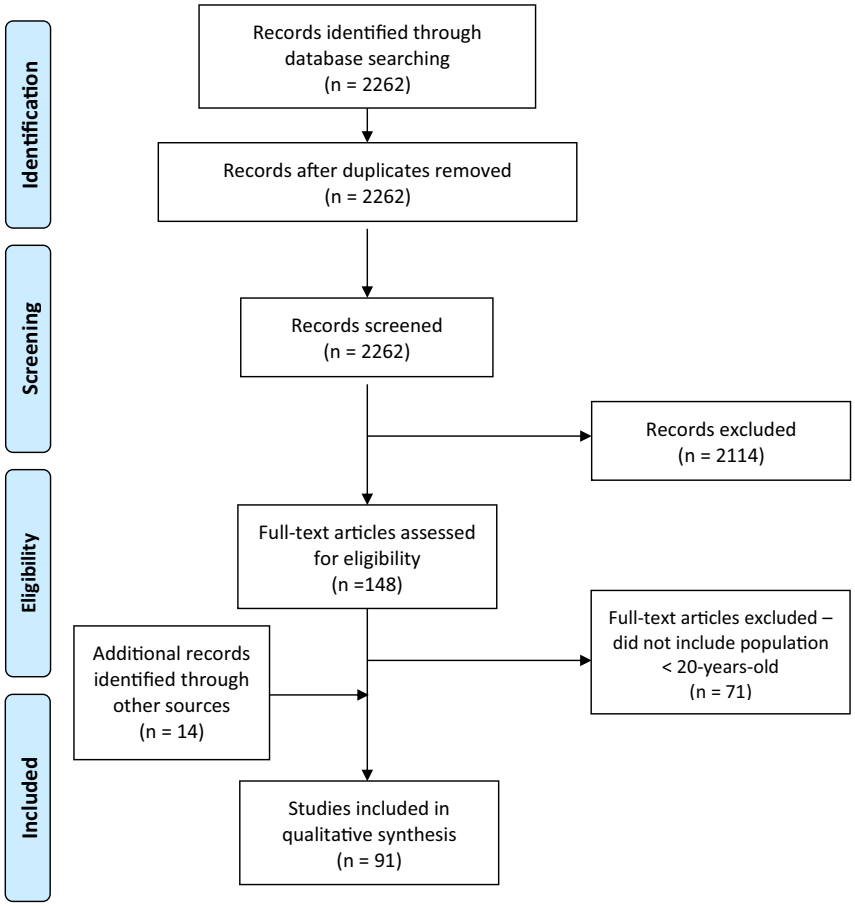

Fig. 1. PRISMA Flowsheet.

exploration to gain hemostasis [21,22]. Both patients in these studies underwent a partial oophorectomy.

Twenty-one studies had a mixed pediatric/adult population, but did not have specific extractable data for children under the age of 20 who underwent OTC. There were 3591 patients represented with ages ranging 0.5 to 44 years old [17,18,20,23–53].

2.3.2. Oocyte harvest

Nine studies had extractable data for children under the age of 20 who underwent oocyte harvest for fertility preservation (Table 2). There were 20 patients with ages 13 to 20 years old. Seventeen patients underwent a standard hyperstimulation protocol. Two patients underwent a trial of a dual stimulation protocol including both luteal and follicular phase stimulation. One of these patients carried a diagnosis of aplastic anemia and required platelet transfusion prior to oocyte retrieval [54]. A 20-year-old with chronic myelogenous leukemia underwent emergency in vitro fertilization (IVF) for attempt at embryo cryopreservation [55]. Gunasheela et al reported a 16-year-old female with Hodgkin's lymphoma who underwent oocyte retrieval prior to OTC. Twelve oocytes and 16 cortical strips were cryopreserved for the patient's future use [56]. A 13-year-old peripubertal girl with Tanner 3 breast development yet premenarchal was able to undergo hyperstimulation. Twenty oocytes were retrieved, eight were metaphase II (MII) at the time of harvest and 10 out of 12 of the metaphase I (MI) oocytes were able to be matured and cryopreserved utilizing *in vitro* maturation (IVM) [57]. Lastly, Brezina et al report a case of a 20-year-old female who underwent oocyte retrieval prior to oophorectomy for a suspected germinoma. She had previously undergone a unilateral salpingo-oophorectomy, omentectomy, pelvic and para-aortic lymph node dissection for a stage IA dysgerminoma [58]. One institution reported an 18-year-old patient who experienced moderate ovarian hyperstimulation syndrome and developed abdominal ascites and required a three-day hospitalization for supportive care for nausea and vomiting as a result of her ovarian stimulation [59].

Seven studies had a mixed pediatric/adult population, but did not have specific extractable data for children under the age of 20 who underwent oocyte harvest. There were 815 patients represented with ages ranging from 2 to 43 years old [20,23–28].

2.3.3. Ovarian transposition/oophoropexy

Six studies had extractable data for children under the age of 20 who underwent ovarian transposition representing 37 patients [44,60–64]. Twenty-seven patients underwent transposition of the ovary as their only fertility preservation method, while 10 patients had transposition of the contralateral ovary during the time of OTC. One study reported four complications associated with ovarian transposition including small bowel obstruction, dyspareunia after retro-uterine transposition, functional ovarian cysts, and pelvic adhesions causing tubal obstruction [60].

2.4. Fertility and hormone restoration procedures

Thirty-eight studies were identified that addressed restoration of fertility and hormone function. Of these reports, 16 provided specific data on fertility and hormone restoration for patients who were 20 years old or younger at the time of OTC. The remainder of the studies were mixed population studies, institutional duplicates, or review articles. The 16 studies with pediatric-specific data represented 20 females who underwent fertility restoration. Eighteen females underwent auto-transplantation of thawed cortical tissue (Table 3) and two patients had

Table 1
Pediatric-specific cases of ovarian tissue cryopreservation [14–17,19–22,25,56,62,63,82,83,88,93,97–103].

Source (Country of Origin)	No. of Patients	Age (range, years)	Patients < 13 years of age	Oophorectomy	Wedge Resection/Partial Oophorectomy	Complications
Rodriquez-Wallberg et al, 2016[a] (Nordic)	248	3-17	21	98[b]	37[b]	minor bleeding
Dolmans et al, 2018 (Belgium)	58	0.8-15.8	21	20	38	none
Jensen et al, 2017 (Denmark)	176	0.6-17.1	29	NA	NA	none
Demeestere et al, 2018* (Belgium)	107	0.5-20	50	66	41	none
Rowell et al, 2018* (USA)	84	0.4-20	46	84	0	none
Lima et al, 2014 (Italy)	54	13 (median)	NA	0	54	major bleeding
Biasin et al, 2015 (Italy)	47	2.7-20.3	24	0	47	none
Poirot et al, 2007 (France)	47	0.8-18	47	47	0	none
Abir et al, 2016 (Israel)	42	2-18	16	27	15	none
Chambon et al, 2016 (France)	36	2-19	16	1	35	major bleeding
Babayev et al, 2012 (USA)	28	2.3-20	NA	28	0	none
Duncan et al, 2015 (USA)	24	2-17	10	14	10	none
Revel et al, 2009 (Israel)	19	5-20	3	19	0	none
Andersen et al, 2008 (UK)	16	5.4-20.4	5	0	16	none
Gracia et al, 2012 (USA)	12	8-20	4	0	12	none
Segers et al, 2015 (Belgium)	8	0-19	6	8	0	none
Huser et al, 2012 (Czech Republic)	4	13-20	0	0	4	none
Meirow et al, 2016 (Israel)	4	14-19	0	3	1	none
Gunasheela et al, 2014 (India)	1	16	0	NA	NA	none
Lawrenz et al, 2011 (Germany)	1	18	0	NA	NA	none
Huang et al, 2008 (Canada)	1	18	0	0	1	none
Povoa et al, 2016 (Portugal)	1	18	0	0	1	none
Bath et al, 2004 (UK)	1	15	0	0	1	none

* up-to-date participation confirmed via personal communication.
[a] Nordic institution represented with duplicate data from Denmark removed from overall cohort.
[b] 113 patients without a clearly described operative technique.

reported fertility restoration outcomes of oocyte harvest and embryo [51,53] cryopreservation prior to receiving gonadotoxic therapy.

Twenty-one studies were identified as mixed population studies, institutional duplicates, or review articles [16,20,29,32,34,41,42,52,56,65–76].

2.4.1. Auto-transplantation of thawed cortical tissue

For the 18 patients who underwent ovarian cortical tissue transplantation, the median age at the time of OTC was 19 years (IQR 14.75-19.75), while the median age at time of auto-transplantation was 24 years (IQR 23-29). Three patients were prepubertal at the time of OTC of whom one went on to have auto-transplantation of her ovarian tissue that resulted in a live birth and two of whom were in biochemical menopause after gonadotoxic treatment and had their auto-transplanted ovarian tissue assist with their pubertal transition [53,77,78]. A 13-year-old patient who was peri-pubertal, yet premenarchal, at the time of OTC underwent ovarian tissue transplantation at 23-years-old resulting in two spontaneous pregnancies and live-births. The ovarian function restoration was still observed up to 7 years after graft placement [51]. The median time between OTC and transplantation was 8.7 years (IQR 6.5-10). The most common transplantation sites were onto or within the remaining ovary and/or within a peritoneal bursa. Restoration of reproductive endocrine hormone function was attained in 94% (17/18) of reported cases. A total of 16 patients had ovarian tissue auto-transplanted for the purpose to restore fertility, of which 69% (11/16) were able to achieve pregnancy and 56% (9/16) resulted in a live birth. One patient conceived two spontaneous pregnancies resulting in two live births from one auto-transplantation [51]. Six of 10 live births (60%) were conceived spontaneously, while the remaining four live births and one ongoing pregnancy were facilitated using assisted reproductive technologies [79–82]. Overall, assisted reproductive technologies, such as IVF, were utilized by 56% (9/16) of patients wanting to achieve pregnancy. One patient underwent IVF for embryo cryopreservation because of the uncertain duration of her ovarian graft function [83].

There were three cases of reported short ovarian graft function or graft failure which lead to re-transplantation of additional thawed cortical tissue in two out of the three patients with only one resulting in a live birth [80,82]. One patient described by Meirow et al was unable to

Table 2
Pediatric-specific cases of oocyte cryopreservation [54–59,75,85,87].

Source (Country of Origin)	No. of Patients	Age (range, years)	Diagnosis	Duration of treatment, *days*	Oocytes Retrieved (range)	Mature Oocytes Cryopreserved (range)	Complications
Lavery et al, 2015 (UK)	8	14-18	sickle cell anemia	11	14.88	12.13	OHSS
Kutteh et al, 2018 (USA)	3	14-16	medulloblastoma	10-12	18-26	12-23	None
Nagashima et al, 2005 (Japan)	2	17-18	AML/ALL	NA	0	0	No oocytes retrieved
Tsampras et al, 2017 (UK)	2	17	aplastic anemia, myelodysplasia	10-14	20-22	13-21	None
Gunasheela et al, 2014 (India)	1	16	Hodgkin's lymphoma	NA	12	7	None
Courbiere et al, 2013 (France)	1	20	CML	11	5	5	25% oocyte survival rate after thawing
Doshida et al, 2013 (Japan)	1	20	ALL	NA	11	10	None
Brezina et al, 2015 (USA)	1	20	dysgerminoma w/ previous oophorectomy	11	45	36	None
Reichman et al, 2012 (USA)	1	13	myelodysplasia	9	20	8 (10)	None

a OHSS – ovarian hyperstimulation syndrome.

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successfully stimulate for oocyte retrieval with her first two frozen-thawed grafts, therefore underwent a third ovarian tissue transplantation procedure. She then underwent four rounds of IVF with her third transplant which resulted in the retrieval of two oocytes harvested. Two embryos were created and transferred which resulted in the live birth of a healthy singleton [82]. There was one report of a patient who spontaneously conceived after transplantation of ovarian tissue but it resulted in a tubal pregnancy [84]. Van DerVen et al also describe five cases of ovarian cortical tissue auto-transplantation (one 17-year-old and four 20-year-olds) that were unsuccessful and did not result in pregnancy or a live birth [84].

2.5. Oocyte harvest and embryo transfer

Two studies included detailed information on live birth outcomes after oocyte cryopreservation that occurred in two 20-year-old female patients. Courbiere et al reported a case of a 20-year-old female diagnosed with chronic myelogenous leukemia who underwent emergency IVF with retrieval of five oocytes. Four embryos were cryopreserved, but only one survived the thawing process. One embryo was transferred and did not result in a pregnancy [55]. Doshida et al reported a case of a 20-year-old female with acute lymphoblastic leukemia who underwent two rounds of controlled ovarian hyperstimulation prior to bone marrow transplant. Ten oocytes were retrieved and vitrified. The oocytes were stored for 59 months prior to warming and intracytoplasmic sperm injection. Two embryos were transferred resulting in the delivery of a healthy singleton baby girl [85]. No data was available on the outcomes of oocytes harvested and vitrified in adolescent patients.

3. Discussion

Fertility preservation has been cited as a quality of life measure for survivors of childhood cancer [2]. Currently, there are both clinically approved and experimental fertility preservation options available to female children 20 years of age and younger who are at risk for premature ovarian insufficiency or future infertility due to gonadotoxic medical therapies. Options for fertility preservation are dependent on the pubertal status of the child, as well as the urgency of medical treatment initiation. This systematic review highlights the large cumulative cohort of pediatric-aged patients, with a wide variety of diagnoses and treatments, who have undergone fertility preservation procedures such as OTC, oocyte cryopreservation, and/or ovarian transposition. It also demonstrates that fertility and hormone restoration experience for patients who were 20 years of age or younger at the time of fertility preservation remains limited.

The ASRM considers oocyte and embryo cryopreservation as non-experimental fertility preservation options for post-pubertal females who find themselves at risk for future premature ovarian insufficiency or infertility [86]. Post-pubertal females are able to physiologically respond to the ovarian hyperstimulation that is required to produce and cryopreserve oocytes for future use. However, this option is not available to prepubertal girls given their lack of hormonal maturity, so their only option to preserve fertility is removal of ovarian tissue for cryopreservation. OTC may also be the only fertility preservation option for post-pubertal girls who cannot delay initiation of their medical therapy given that ovarian hyperstimulation may take upwards of 14 days to complete [54–59,75,85,87].

In the majority of publications reviewed, OTC was offered to children with a variety of medical and oncologic diagnoses as an experimental fertility preservation option under a research protocol. Enrollment qualifications were often reserved for patients at significant risk of gonadotoxicity secondary to planned radiation and chemotherapy, including regimens involving alkylating chemotherapy agents, whole abdomen irradiation, and stem cell transplantation conditioning. However, Jadoul et al report offering OTC to patients, including those of pediatric age, at any risk of future premature ovarian insufficiency and infertility [62]. A few institutions have incorporated OTC into standard clinical care for adult women receiving gonadotoxic therapy while designating OTC as experimental for children under 18 years old due to the paucity of reproductive outcomes for fertility restoration [20].

Pediatric specific literature and collected institutional data suggest that over 1,000 children 20 years of age and younger have undergone OTC as a means of fertility preservation. Interestingly, most institutions that offer OTC service a wide age range of patients from children to adults. Pediatric patients often do not carry the same diagnosis or undergo the same treatment regimens as adult women. They may also pose unique perioperative, anesthetic, surgical, and post-operative needs [88]. A wide range of operative practices for OTC, including variations in operative approach and technique, have been reported in adult women undergoing fertility preservation surgery [89]. This study further highlights the lack of standardization for ovarian cortical tissue removal in children. In patients 20 years old and younger, there was no standard amount of ovarian cortical tissue removed for cryopreservation across or even within institutions. Many experts in the field argue the need for oophorectomy for prepubertal children or girls at the greatest risk for infertility to preserve the maximal amount of ovarian tissue for cryopreservation purposes. Despite the lack of a standard technique, oophorectomy and ovarian cortical wedge biopsy have been shown to be a low-risk operative procedures, with only three publications citing cases of perioperative bleeding resulting in transfusion or reoperation. All instances of major bleeding requiring transfusion or re-operation were associated with partial oophorectomy [20–22]. Another option for pediatric fertility preservation is oocyte aspiration and IVM at the time of OTC for the purposes of isolating immature oocytes (MI) and maturing them *in vitro* to fertilizable MII oocytes. This technique was reported in 71 children with variable success, and IVM of oocytes by this method still remains in its infancy [14–19].

Oocyte cryopreservation was deemed a non-experimental fertility preservation method by the ASRM in 2013 [12]. Despite its success in adult women, there remains a limited number of publications that discuss hyperstimulation and oocyte retrieval for post-pubertal children receiving fertility-threatening therapy [54–59,75,85,87]. We identified 20 patients under 20 years old who underwent oocyte cryopreservation prior to initiation of gonadotoxic treatments. Of those cases reported, the time for hyperstimulation prior to oocyte retrieval ranged between 10-14 days. Prompt initiation of cancer therapy may be required for some children and therefore delaying treatment for upwards of two weeks for fertility preservation may not be feasible. These children may be better served by undergoing OTC given the minimal post-operative delay to therapy [88]. The youngest patient reported to successfully undergo oocyte retrieval and cryopreservation was 13 years old [87]. In addition, there has been a wide range of success in terms of the number of MII oocytes cryopreserved in these children [54–59,75,85,87]. The majority of oocytes were cryopreserved on initial retrieval, but there have also been reports of successful IVM of immature oocytes in these adolescent patients [57]. Of note, ovarian hyperstimulation syndrome was reported in an adolescent patient which postponed oocyte retrieval and significantly delayed the patient's planned cancer treatment. In addition, pre-procedural optimization may be required for patients with hematologic disturbances, including the need for blood product transfusion.

Ovarian transposition was highlighted in very few cases and utilized most often in patients receiving pelvic and/or spinal irradiation. Transposition may protect the ovary from direct radiation therapy but does not protect from systemic effects of chemotherapy. It can be successfully performed as an adjunct at the time of OTC if the contralateral ovary is anticipated to be in the planned radiation field. Conclusions about the efficacy of ovarian transposition cannot be drawn from this study but there are long-term survivor studies that suggest it may not be an effective means of fertility preservation on its own [90].

Very few cases of successful auto-transplantation of ovarian cortical tissue that was procured prior to the age of 20 years old have been

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Table 3
Ovarian tissue auto-transplantation of cortical tissue that was harvested and cryopreserved in childhood [51,53,68,77,78,80–84,91–94].

Source (Country of Origin)	No. of Patients	Age at OTC	Prepubertal at OTC	Diagnosis	Treatment	Age at Transplant	Transplant Site	Hormone Restoration	Pregnancy	ART	Live Birth	Re-transplant	Complications	Notes
Demeestere et al, 2015 (Belgium)*	1	13	Yes	sickle-cell anemia	HSCT[a]	23	remaining ovary, peritoneal bursa, subcutaneous tissue	Yes	Yes	No	Yes	No	None	2 live births
Donnez et al, 2011 (Belgium)	1	17	No	metastatic neuroectodermal tumor of orbit	HSCT	24	decorticated bilateral ovaries	Yes	Yes	No	Yes	No	None	
Donnez et al, 2012 (Belgium)	1	18	No	large tubo-ovarian abscess	bilateral salpingo-oophorectomy	24	peritoneal bursa	Yes	Yes	Yes	Yes	No	None	5 cycles of IVF - 5 oocytes harvested - 1 embryo transfer - live birth
Ernst et al, 2013 (Denmark)	1	9	Yes	Ewing sarcoma	42.1 Gy pelvis CED[b] > 25	13.6	remaining ovary	Yes	n/a	n/a	n/a	No	None	post-treatment menopausal levels of FSH - auto-transplanted tissue assisted with pubertal transition and normalization of FSH
Schmidt et al, 2011 (Denmark)	1	19	No	paroxysmal nocturnal hemoglobinuria	HSCT	NA	remaining ovary, subcutaneous tissue	Yes	No	Yes	No	No	None	3 cycles of IVF - 5 oocytes harvested from orthotopic graft and 3 oocytes from heterotopic graft - two embryos transferred - negative bhCG
Poirot et al, 2012 (France)	1	10	Yes	sickle-cell anemia	HSCT	13	subcutaneous tissue	Yes	n/a	n/a	n/a	No	None	post-treatment menopausal levels of FSH - auto-transplanted tissue heterotopically which assisted with pubertal transition, normalization of FSH, and menses
Roux et al, 2010 (France)	1	20	No	sickle-cell anemia	HSCT	23	remaining ovary, peritoneal bursa	Yes	Yes	No	Yes	No	None	
van DerVen et al, 2016 (Germany)	2	20	No	Hodgkin lymphoma	NA	29	peritoneal bursa	Yes	Yes	No	No	No	tubal pregnancy	

		20	No	cystadenofibroma	NA	27	peritoneal bursa	Yes	Yes	No	Yes	No	None	
Meirow et al, 2016 (Israel)	4	19	No	chronic myeloid leukemia	NA	27 (28)	remaining ovary	Yes	No	Yes	No	Yes	short graft survival length (6 mo./4 mo.)	5 cycles of IVF - 7 oocytes harvested - 2 embryos transferred - no live birth
		19	No	Hodgkin lymphoma	NA	35	remaining ovary	Yes	No	Yes	No	No	None	2 cycles of IVF - 4 oocytes harvest - 1 embryo transferred - no live birth
		14	No	Ewing sarcoma	NA	21	peritoneal bursa	No	No	No	No	No	graft failure	
		19	No	acute myeloid leukemia	NA	31	remaining ovary	Yes	Yes	Yes	OG	No	None	2 cycles of IVF -- 6 oocytes harvested -- 4 embryos, 2 transferred -- ongoing pregnancy at the time of publication
Revel et al, 2011 (Israel)	1	19	No	thalassemia	HSCT	23 (25, 26)	remaining ovary, peritoneal bursa	Yes	Yes	Yes	Yes	Yes	graft failure	failed IVF with first two transplants - third transplant underwent 4 cycles of IVF -- 2 oocytes harvested -- 2 embryos transferred - live birth
Biasin et al, 2015 (Italy)	1	20.3	No	thalassemia	HSCT	29	remaining ovary	Yes	Yes	No	Yes	No	None	
Povoa et al, 2016 (Portugal)	1	18	No	heterogeneous mass s/p oophorectomy and congenital absence of contralateral ovary	oophorectomy	28	peritoneal bursa	Yes	No	Yes	No	No	None	underwent IVF -- 2 oocytes harvested -- 1 embryo cryopreserved
Callejo et al, 2013 (Spain)	1	20	No	dermoid cyst, large ovarian cyst	bilateral-oophorectomy	30	peritoneal bursa	Yes	Yes	Yes	Yes	No	None	underwent IVF -- 2 oocytes harvested -- 1 embryo transferred - live birth
Matthews et al, 2018 (Denmark)	1	9	Yes	thalassemia	HSCT	23	remaining ovary	Yes	Yes	Yes	Yes	No	None	underwent IVF – 8 oocytes harvested – 2 embryos transferred – live birth

[a] HSCT = hematopoietic stem cell transplantation.
[b] CED = cyclophosphamide equivalent dose, c OG = on-going.
* Up-to-date participation confirmed via personal communication.

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reported. Nearly all patients that were described had restoration of reproductive hormone function, albeit at varying lengths of graft duration [51,53,68,77,80,81,83,84,91–94]. Over half required use of assisted reproductive technologies to attempt pregnancy [78,80–83,91]. Ten live births have been reported in this group, five of which were spontaneously conceived [51,68,84,92,93]. Amongst them, only two patients experienced fertility restoration after transplantation of ovarian tissue harvested at pre- or peri-pubertal age [51,78]. There are two reports describing the use of auto-transplanted ovarian tissue for the restoration of hormone function to assist with pubertal transition [53,77]. Overall, there is significant heterogeneity of the cryopreservation and transplantation processes.

When all age groups are considered, over 130 live births as a result of ovarian tissue auto-transplantation have been reported [95]. The majority of these successful cases were in women who were 20 to 30-years-old at the time of their OTC with very few representing our patient population of interest [96]. We identified only 13 detailed reports of auto-transplantations resulting in eight live births in patients 20 years of age or younger at ovarian tissue harvest, with only three who had their ovarian tissue frozen prior to menarche. The limited outcomes from thawed ovarian tissue transplant could be secondary to the infancy of OTC programs for children, the potentially long cryopreservation time between tissue harvest and re-implantation given the young age of patients enrolled, or both. In the reviewed studies, we found that the average length of time from ovarian tissue freezing to thawing for re-implantation was nearly 10 years. The success of auto-transplantation in women who were children at the time of OTC may take decades to be fully understood. In addition, while a few institutions did mention unsuccessful transplantations in girls 20 years of age and younger at the time of OTC, there is a risk of reporting bias toward publication of only cases in which fertility and hormone restoration was achieved [82,84].

There are children who receive gonadotoxic therapy prior to menarche who fail to transition through puberty spontaneously due to the side effect of their treatment [97]. Beyond fertility restoration, ovarian tissue auto-transplantation may provide an option to restore reproductive hormone function to assist children through the pubertal transition without exogenous hormones. Normalization of post-menopausal reproductive biomarker levels and successful restoration of hormone function have been accomplished through both orthotopic and heterotopic transplantation of frozen-thawed ovarian cortical tissue [53,77]. Ernst et al orthotopically transplanted 20% of the patient's stored cortical tissue while Poirot et al heterotopically transplanted 3 out of the patient's 23 frozen cortical strips in order to induce puberty and menarche in two 13-year-old girls with abnormal sexual development [53,77]. Both patients had nearly two years of ovarian graft function which allowed for appropriate pubic and breast development. The remainder of the patient's frozen cortical strips could then be used for future fertility restoration.

The pregnancy (69%) and live birth (56%) rates in our population of interest were higher than the 57.5% pregnancy and 37.7% live birth rates presented in a meta-analysis by Pacheco et al. that looked at 309 ovarian tissue transplants in 255 women [96]. As found in our study, the majority (62.3%) of pregnancies reported in the meta-analysis were conceived spontaneously without the use of ART [96]. One factor not studied in the meta-analysis was the overall use of ART to attempt pregnancy. We found that over fifty-percent of patients utilized ART to attempt pregnancy, of which half conceived and just over one-third resulted in a live birth. Those who failed to achieve pregnancy following ART either underwent multiple rounds of IVF, had low numbers of oocytes retrieved, and/or had unsuccessful embryo transfer [82,83,91]. These data may prove to be useful in counseling patients and their families about what future fertility restoration may involve clinically and financially. While the pregnancy and live birth rates are higher in patients 20 years old and younger at the time of OTC as compared to the overall data on ovarian tissue transplant, the number of patients is small and may bias the results. In addition, only two live births have been reported in the published literature from ovarian tissue that was procured in a pre- and peri-pubertal child [51,78]. The efficacy of fertility restoration in patients who are prepubertal at the time of OTC cannot be determined at this time.

Lastly, while this study was not designed to compare the efficacy between auto-transplantation sites, there were spontaneous live births reported from orthotopically transplanted tissue on both the ovary and within a peritoneal bursa, but not from exclusive heterotopic transplantation of ovarian cortical tissue [51,68,80,93]. Successful IVF and oocyte retrieval was also documented from both orthotopic sites [81,82,84,92]. Restoration of reproductive hormone function was documented and achieved in all orthotopic and heterotopic positions [53,68,77,79].

There are several limitations to this systematic review. First, the majority of data on fertility and hormone preservation and restoration is based on single-institution, retrospective case series. Despite the increasing awareness of fertility preservation options available to pediatric patients and expanding participation in fertility preservation programs, the number of patients undergoing OTC and auto-transplantation remain low, especially in children. Second, prolific fertility preservation centers have published multiple case series over the past decade with likely overlapping patient cohorts. Consequently, there may be the possibility of duplicate patient records and overestimation of the number of overall OTC procedures. We made significant efforts to identify the most recent data in published case series and to obtain up-to-date institutional data via direct communication with authors from centers with extensive fertility preservation experience to minimize the risk of duplicate data. Third, there were numerous publications with mixed populations for which pediatric specific data could not be extracted, therefore we were unable to capture ovarian tissue and oocyte cryopreservation cases for children under 20 years old in those instances. In terms of ovarian tissue auto-transplantation, there may be reporting bias towards successful cases rather than transplantation failures. Lastly, there are many additional considerations surrounding fertility preservation for children including, but not limited to, the risk of re-implanting malignancy, effects of pelvic irradiation on pregnancy, ovarian graft survival duration, and comparison of transplant site efficacy, but these are beyond the scope of this systematic review.

4. Conclusion

Clinically accepted and experimental fertility preservation options such as OTC, oocyte cryopreservation, and ovarian transposition are available to female children and adolescents who are at risk for premature ovarian insufficiency and infertility due to gonadotoxic treatments. There is a large cohort of pediatric-aged patients, with a wide variety of diagnoses and treatments, who have undergone fertility preservation. Currently, fertility and hormone restoration experience for patients who were 20 years old or younger at the time of fertility preservation remains limited. There should be increasing efforts at pediatric institutions to further refine and offer fertility preservation technologies to all patients undergoing gonadotoxic therapies. Multi-institutional collaborative efforts, such as the Pediatric Initiative Network of the Oncofertility Consortium are needed to continue to improve care for children at risk for infertility due to gonadotoxic therapy.

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