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Review

Safety and Efficacy of Ovarian Tissue Autotransplantation: a Systematic Literature Review

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Abstract

Ovarian tissue autotransplantation is an innovative fertility preservation technique that has provoked ongoing investigations. The purpose of the present study was to assess the safety and reproductive performance of ovarian tissue autotransplantation. This review is conducted according to PRISMA guidelines. Seven studies met the inclusion criteria. A total of 3427 patients underwent ovarian tissue cryopreservation and 205 received an autotransplantation. Tissue retrieval was mainly performed by laparoscopy and only one major complication occurred. Transplantations were predominantly performed by open procedures and data on safety were insufficient. A total of 295 autotransplantations were analyzed, resulting in 104 pregnancies. Sixty-five pregnancies led to live births, while nine were ongoing at that time. A pregnancy rate (PR) of 50.7% and a live-birth rate (LBR) of 32.7% were observed. Natural conception accounted for 46.3% of live births. No birth deficits were recorded. Ovarian tissue autotransplantation seems to be a safe procedure with acceptable pregnancy rates.

Keywords

autologous, cryopreservation, assisted, fertility preservation, live birth, transplantation, reproductive techniques

INTRODUCTION

Fertility preservation (FP) has become a field of major interest in the recent years.[1-3] Cancer is the main indication, but several non-oncologic conditions and associated therapies may also have adverse sequelae on future fertility.[1] Oocyte and embryo cryopreservation are available for fertility preservation in post-pubertal women.[2,4] These are methods dependent on controlled ovarian stimulation (COS), a process that necessitates post-pubertal status and adequate time for the procedure to be completed before initiation of gonadotoxic therapy.[4]

On the contrary, FP procedures independent from controlled ovarian stimulation are the only option in prepubertal status, hormone-dependent malignancies or aggressive tumors, in need for immediate intervention.[2] Ovarian tissue cryopreservation (OTC) and autotransplantation after thawing has been described as an experimental possibility in the late '90s.[5] In 2004, the report of the first live birth after ovarian tissue autotransplantation in humans by Donnez et al. encouraged further research.[6]

The classification of OTC as experimental or established is strongly debated under the light of emerging evidence.[1,4,7] According to the current data, the num-

ber of babies born after ovarian tissue transplantation techniques may exceed 200.[8] The purpose of the present study was to review and summarize the current knowledge and experience on ovarian transplantation on 1) fertility outcomes (pregnancy rates, live births, early pregnancy complications) and 2) procedural surgical safety of tissue harvesting and transplantation. A special focus is given to procedure-related complications that are under-investigated.

MATERIALS AND METHODS

Search strategy

The search protocol used in the present study is in accordance with the guidelines for Systematic Reviews and Meta-analyses, as reported in PRISMA.[9] Two reviewers (EG, VK) independently searched medical databases (Pubmed, Clinicaltrials.gov) for eligible studies. Original studies that investigated fertility outcomes (pregnancies, live births) following human ovarian tissue autotransplantation were included in the present study. Studies with fewer than 10 subjects were excluded from the review, as well as studies not written in English language.

Data sources and search strategy

The Pubmed (1966-2019) and Clinicaltrials.gov were searched for eligible studies. The independent researchers used a standardized search protocol with the following combination of key words: (ovarian tissue transplantation AND pregnancy) OR (ovarian tissue transplantation AND fertility). **Fig. 1** displays the 'PRISMA' flow diagram. The characteristics of the patients and the studied outcomes are listed in **Tables 1, 2.**

Outcomes measures

The primary outcome measures were pregnancy rates, live births, and early pregnancy complications associated with ovarian tissue transplantation as well as surgical complications during harvesting and transplantation of the tissue. As secondary outcome measures, the presence of birth deficits, the route of delivery and prematurity were assessed.

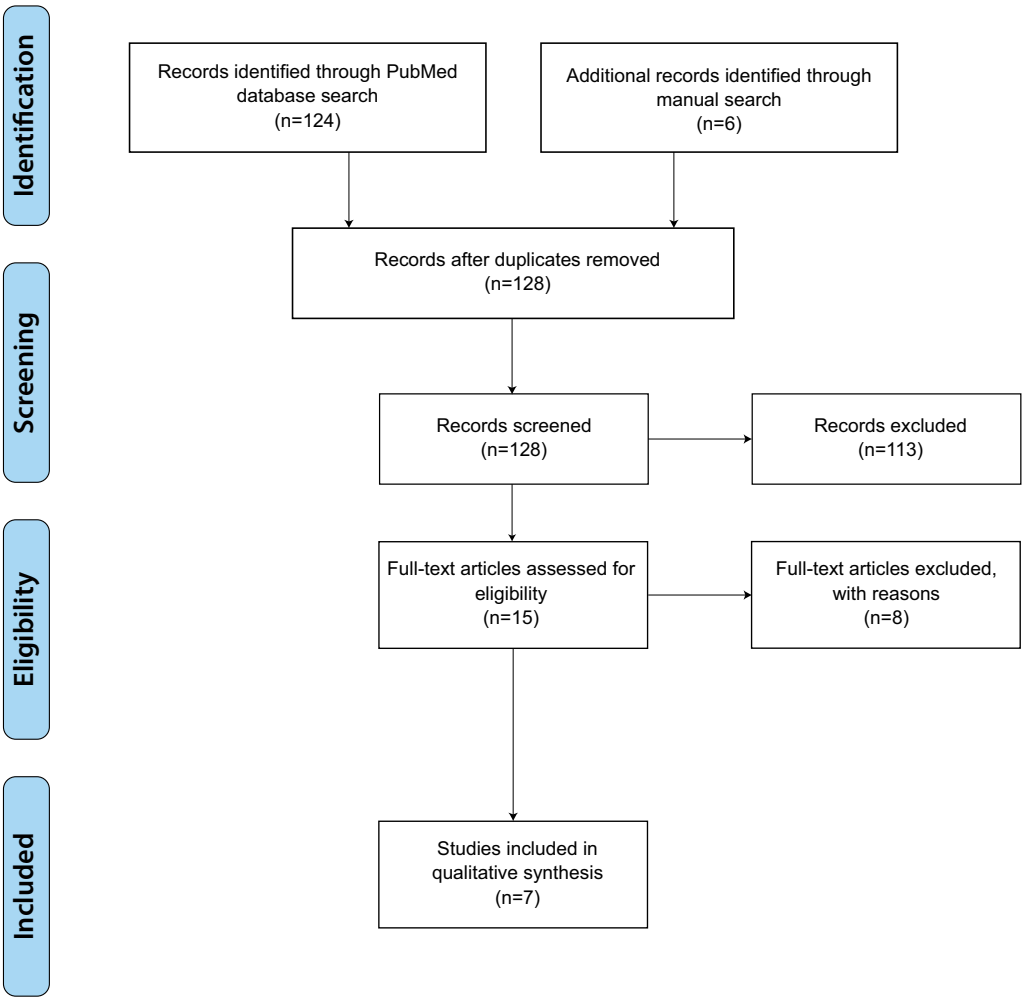

Figure 1. PRISMA flow diagram.

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Table 1. Characteristics of the included patients, the procedure and the complications associated with tissue retrieval and transplantation

First author	Indication for FP (NOP OTC[a])	Age at retrieval [b]	NOP OTT[c]	Approach for retrieval	Surgical procedure	Complications retrieval	Approach for transplantation	Complications transplantation	Size of transplants	Location
Schmidt et al. (2011)	Malignancy (393)	NA[d]	3%	NA	NA	NA	LAP[f] or MLT[g] (11) or LT[h] (1)	NA	5×5×(1-2) mm	Ortho[i] (5) Hetero[j] (1) Both[k] (6)
Dittrich et al. (2015)	Malignancy (20)	30.5 (20-37)	100%	LAP	Partial ovariectomy	NONE	NA	NA	3×3×1 mm	Ortho
Jensen et al. (2015)	Malignancy or benign conditions (41)	29.8 (9.5-38.7)	100%	NA	NA	NONE	NA	NA	5×(5-10)×(1-2) mm	Ortho (15) Hetero (6) Both (20)
Rodriguez-Wallberg et al. (2016)	Malignancy or benign conditions (1608)	NA	2.9%	LAP	Unilateral oophorectomy. Ovarian biopsies Both	Only minor (bleeding)	NA	NA	NA	Ortho Hetero (1) Both
Meirow et al. (2016)	Malignancy (20)	28.8(14-39)	100%	LAP	unilateral or bilateral oophorectomy	NA	MLT	NA	5×10× (1-2) mm	Ortho
Jadoul et al. (2017)	Malignancy or benign conditions (545)	22.3±8.8[e]	3.9%	LAP or LT	NA	5 minor, 1 major (bleeding)	NA	NA	NA	Ortho
Diaz-Garciaz et al. (2018)	Malignancy (800)	34.3±7.2	5.5%	LAP (738) or MLT (32) or LT(30)	NA	NA	LT (41) LAP (1)	NA	NA	Ortho
Overall mean values	3427	29.5±7.8	45%	LAP 93% MLT 3.6% LT 3.4%		Overall: 0.3% Major: 0.05% Min or: 0.27%	LAP or MLT 43.2% LT 56.8%			Ortho: 79.1% Hetero: 4.4% Both: 16.5%

[a] NOP OTC: Number of patients that underwent ovarian tissue cryopreservation; [b] Ages are presented as mean either with range inside the parenthesis (range) or with standard deviations (±SD); [c] NOP OTT: Number of patients that underwent ovarian tissue transplantation, as percentage of the total number of patients that received a transplant and was included in the study; [d] NA: Not addressed; [e] The mean age and standard deviation refer to the whole cohort that underwent OTC, not the subgroup of the patients that received autotransplantation; [f] LAP: Laparoscopy; [g] MLT: Minilaparotomy; [h] LT: Laparotomy; [i] ORTHO: Orthotopic autotransplantation; [j] HETERO: Heterotopic transplantation; [k] BOTH: Orthotopic and heterotopic autotransplantation were simultaneously performed.

Table 2. Fertility outcomes in the population of patients that received ovarian transplants

Author	NOP[a] (Re-transplantations)	CP[b]	NOP ART[c]	Method ART	Live birth	Early pregnancy complications	Ongoing pregnancy	Pregnancies
Schmidt et al.	12 (5)	SF	10	IVF[d]/ICSI[e]	3	2 biochemical, 1 miscarriage	-	6
Dittrich et al.	20	SF	1	IVF	4	1 miscarriage	4	9
Jensen et al.	41 (12)	SF	NA	IVF	13 (1 twin)	9 miscarriage, 2 abortions , 4 biochemical	1	28
Rodriguez-Wallberg et al.	47 (72)	SF	7	IVF/ICSI	17	1 ectopic	2	20
Meirow et al.	20 (1)	SF	14	IVF	10 (1 twin)	1 biochemical , 1 ectopic, 3 miscarriages	2	16
Jadoul et al.	21	SF	0	-	10	NA	0	10
Diaz-Garciaz et al.	44	SF	28	NA	10	5 30 complications reported (28.8% of total pregnancies)	0	15
					67 (65 pregnancies , 2 twin gestations) LBR[e] 32.7%	7 (6.7 %) biochemical, 14 (13.5 %) miscarriages, 2 (1.9%) abortions, 2 (1.9%) ectopic, 5 (4.8%) not classified		104 PR[f] 50.7%
TOTAL	205 (90)	SF 100%	>60				9 (8.7%)	

[a] NOP: Number of patients that received a transplant; [b] CP: cryopreservation technique; [c] ART: Assisted Reproduction Technology; [d] IVF: In-vitro fertilization; [d] ICSI: Intracytoplasmic sperm injection; [e] Number of infants born alive, beyond the threshold of viability over 24 weeks of gestational age per patient; [f] Number of pregnancies diagnosed by β-HCG elevation per patient.

RESULTS

Excluded studies

According to the present search protocol, fifteen studies were considered for inclusion in this review. The reviewers assessed all of them for eligibility. Finally, seven studies fulfilled the inclusion criteria for participation in the present analysis. The eligible studies included a total of 3427 patients that underwent ovarian tissue harvesting and cryopreservation for future use. A total of 205 patients had been subjected to ovarian tissue autotransplantation and their outcomes are analyzed in the present review. Four of the included studies were retrospective in design[10-13], two were prospective non-comparative[14,15], and one was prospective comparative[16] comparing oocyte vitrification to ovarian tissue freezing[16].

Characteristics of the included patients

A total of 3427 patients were subjected to ovarian tissue retrieval and cryostorage for fertility preservation, mainly due to malignancy. Some studies, also, included patients diagnosed with non-oncologic conditions such as hematologic, immunologic/systematic[10,11,13], genetic[12,13] or benign / borderline ovarian pathology.[13] Mean age of patients was 29.5±7.8 years.

Characteristics of the grafts and the techniques used for tissue retrieval and transplantation (approach, location)

Ovarian tissue was mainly retrieved by laparoscopy (93%). Two studies described ovarian tissue harvesting by laparotomy or minilaparotomy (3.4% and 3.6%, respectively).[13,16] Type of surgery for ovarian tissue retrieval varied among partial ovariectomy, unilateral or bilateral oophorectomy and ovarian biopsies. Fewer data are available on the procedure and complications encountered in tissue transplantation. Only three studies report the approach used for transplantation (laparoscopy, minilaparotomy or laparotomy).[11,15,16] Among those providing quantitative data, transplantation was performed in 56.8% by laparotomy and in the remaining 43.2% by laparoscopy or minilaparotomy.[11,15,16]

The grafts used for transplantation varied in dimensions, but what was common was a minimum thickness of 1 mm of cortex.[10,11,14,15] Orthotopic transplantation was the prevalent choice (79.1%).[13-16] Alternatively, both orthotopic and heterotopic transplantations were performed simultaneously (16.5%). Only 8 cases of exclusive heterotopic transplantation are reported in these studies, resulting in 4.4% of the total cases.[10-12] The results are presented in **Table 1**.

Primary outcome measures

As far as ovarian tissue retrieval is concerned, two studies reported no complications during the procedure.[10,14] Rodriquez-Wallberg et al. reported only minor complications (such as minor bleeding) in laparoscopic tissue retrieval.[12] Jadoul et al. described several minor complications such as fever, labial hematoma, urinary infection, bowel irritation, psychological distress and one major complication (bleeding) during the retrieval.[13] The overall complications rate was 0.3%. Data on procedure-related complications are not available regarding ovarian tissue transplantation.

A total of 295 transplantations are included in the present analysis. Ninety out of the 295 transplantations were re-transplantations due to diminished function of the first transplant, aiming either to ovarian endocrine function restoration or pregnancy. In all included studies, the ovarian tissue autografts were preserved by the slow-freezing technique. In the study of Jadoul et al., no assisted reproduction techniques were used, and all live births recorded constitute natural conceptions.[13] Jensen et al. did not provide sufficient quantitative data on the number of patients that were subjected to assisted reproduction techniques in their population, while Diaz-García et al. did not specify the type of ART technique used.[10-16]

A total of 104 pregnancies were achieved between 295 transplantations. A total of 205 patients received a transplant, leading to a pregnancy rate of 50.7%, including re-transplantations. Sixty-five of them (62.5%) resulted in 67 live births, including two multiple pregnancies (twins), leading to live-birth rate of 32.7%. Nine of them (8.7%) were ongoing by the time the studies were published. The remaining 30 pregnancies (28.8%) did not proceed due to early pregnancy complications or legal termination or unclassified etiology, as presented in **Table 2**. Among six studies that provided sufficient data concerning the origin of pregnancies (ART or natural conception) that resulted in live births, including 242 transplantations, 28 pregnancies or 29 live births (including 1 twin pregnancy) resulted from ART and 25 from natural conception. As a result, ART accounted for 53.7% of live births among these patients, while natural conception - for the rest 46.3%.

Secondary outcome measures

As far as secondary outcomes are concerned, the data provided by the existing studies are sparse. The prevalence of prematurity among neonates born after ovarian tissue transplantations has not been studied so far. Only two studies provided limited data on prematurity. Among 13 live births, nine of them proceeded to term gestations (69.2%). Birth defects were not recorded. Schmidt et al. provided some insight on the obstetrical outcome of pregnancies after ovarian transplantation. The study reported three term pregnancies, one of which was complicated by preeclampsia.[11] The birth weight was estimated to be from 2600 to 3828 g.

DISCUSSION

The aim of the present study was to assess the safety and efficacy of ovarian tissue transplantation, in terms of fertility performance and procedural safety. Safety outcome measures were focused on procedure-related complications. Data on procedure-related complications associated with tissue transplantation are under-reported in the current literature. Overall surgical complication rate for tissue retrieval was 0.3%. Ovarian transplantation was associated with a pregnancy rate of 50.7% and a live birth rate of 32.7% per patient.

Growing follicles are the most vulnerable to the cytotoxic effects of chemotherapy.[17] The main impact in the ovary is cellular death mediated by apoptosis in primordial follicles, due to the interruption of DNA function.[18] The loss of primordial follicles is irreversible.[17] An alternative hypothesis supports that primordial follicles are exhausted due to their increased recruitment from the "resting pool" secondary to the growing follicles depletion. Nevertheless, indirect effects on the ovary are attributed to decreased vascularization and subsequent ischemia and cortical fibrosis.[17,18] Ionizing radiotherapy is an important part of cancer therapy.[19] Resting follicles do not demonstrate high mitotic division rates. However, even in that case, the human oocyte is extremely radiosensitive.[19]

Radiation induces histologic changes in the uterus such as endometrial atrophy, myometrial fibrosis, and devascularization.[19,20] Apart from the effects on the ovarian reserve and function, the application of high dose radiation during childhood promotes permanent changes to the myometrium and its distensibility, as well as the uterine vasculature.[20] Those changes are associated with a higher risk for complications including implantation/placentation disorders, miscarriage, pretermaturity, and low birth weight, especially in the context of assisted reproduction.[19,20]

Chemotherapy has a negative impact on oocyte number and quality and the significance for ovarian tissue cryopreservation before initiation of gonadotoxic therapy has been highlighted, especially in the subgroup of patients aged over 15 years.[21-24] However, this may not be feasible in several clinical scenarios. Nevertheless, the exact impact of chemotherapy (and particular regimens) on fertility outcomes, when applied prior to cryopreservation, has not been fully investigated. There is some evidence that specific non-alkylating agents do not compromise the number of non-growing follicles in biopsies of human ovaries.[25] Ovarian tissue cryopreservation is generally not contraindicated, even if a course of chemotherapy has preceded the harvesting of the tissue.[26] The clinical impact of those interventions on post-transplantation fertility outcomes is a field of ongoing research.[27]

In the light of new evidence, the American Society for Reproductive Medicine has removed the label experimental and considers ovarian cryopreservation an acceptable option. However, there is a need for further research, espe-

cially concerning the subgroup of pediatric and adolescent populations.[28]

In 2019, Corkum et al. conducted a systematic literature review on fertility preservation after gonadotoxic treatment in this specific subgroup of patients.[29] A total of 1019 patients that underwent OTC were assessed. The median age at retrieval was 19 years and at autotransplantation 24 years and median storage interval was evaluated at 8.7 years. Tissue retrieval was obtained mainly by oophorectomy or alternatively by partial oophorectomy or ovarian biopsies. The procedure was complicated in 3 cases with bleeding. Of cases with major bleeding, one required blood transfusion and another reoperation to surgically achieve hemostasis. Both cases were associated with partial oophorectomy. In all studies that provided relevant data, cryopreservation was carried out with the slow freezing technique. Among 16 patients that sought fertility, a pregnancy rate of 69% and a live-birth rate of 56% was achieved after transplantation. The interesting finding though is that one pregnancy was achieved after OTT of tissue harvested at prepubertal age, and other two pregnancies of tissue harvested at peripubertal age, yet before initiation of menses. All resulted in live births.

In 2008, Bedaiwy et al. published a systematic review of the literature including case reports and small case series concerning the reproductive outcome after OTT.[30] The authors reported a total of nine pregnancies among 25 patients that received a transplant specifically for fertility restoration (no re-transplantations recorded), leading to 0.36 pregnancies per transplantation/individual, which is comparable to the present findings. The re-transplantations may potentially raise the pregnancy chance, although the true origin of these gestations from the grafted tissue remains hypothetical.

In 2018, Diaz-Garciaz et al. conducted a prospective study to compare the efficacy of ovarian tissue transplantation versus ovarian oocyte vitrification with 49 patients undergoing OV compared to 44 patients undergoing OTC.[16] The two techniques did not differ significantly on fertility performance. However, a statistically insignificant increase in clinical pregnancy rate and live-birth rate was observed in favor of oocyte vitrification RR 1.31 (95% CI 0.90-1.92) and RR 1.39 (95% CI 0.95-2.03), respectively. Of note, the authors commented that OTT failed to restore fertility in cases where tissue retrieval took place over the age of 36 years. Nevertheless, even in cases where tissue harvesting was performed before that age, no clinical pregnancies were achieved beyond 36 years. On the contrary, oocyte vitrification resulted in a 30% possibility in achieving pregnancy in this subgroup. Diaz-Garciaz described a percentage of 46.7% of natural conception following ovarian tissue transplantation, which is comparable with the present finding of 46.3%.

Future perspectives and fields for future research

In the clinical setting where controlled ovarian stimulation is not feasible, the possibility of retrieval of immature oocytes (I) from surgical specimens before they are being prepared for cryopreservation)[31,32] or (II) with aspiration from the ovaries, as an independent FP technique[2,33-35] followed by in vitro maturation has arisen. The latter option is also deprived of the surgical complications associated with ovarian tissue grafting and transplantation in non-ovarian malignancies.[35] These oocytes have the potential for in vitro maturation and can, afterwards, be stored as mature oocytes or embryos for use in IVF procedures.[36] A significant advantage of this procedure over ovarian tissue autotransplantation is the elimination of the risk of cancer recurrence by avoiding the transplantation of potentially malignant-contaminated grafts to the host.[31] This experimental approach may 'assist' ovarian tissue cryopreservation or be applied independently, especially in patients with ovarian malignancies, even in the context of surrogacy.[31,32,37]

There should be standardization for the ovarian tissue cryopreservation procedures, regarding both the surgical techniques and the specimen preparation for cryobanking, especially in the subgroup of children and adolescents where this is the only fertility preservation option. It has been demonstrated in animal studies that the use of advanced energy devices for tissue retrieval compromises folliculogenesis, compared to cold dissection.[38] Therefore, there are concerns for the effects of thermal energy and thermal spread that should be further investigated. There is evidence that vitrification may have a more favorable impact on ovarian follicles than slow freezing; however, the clinical implications of those findings remain to be determined.[39] This paucity of knowledge highlights the need for optimization of the techniques for tissue processing, including surgical retrieval, graft preparation, graft size and number, and freezing techniques in order to enhance fertility performance after autotransplantation and provide high quality oncofertility care.[40]

Strengths and limitations

The literature search was conducted by two independent reviewers. The included studies involve a limited number of patients that were finally submitted to OTT. Interestingly, not all women that received a transplant were seeking fertility. Consequently, the efficacy of OTT in terms of fertility may be underestimated from the inclusion of women that did not desire pregnancy. Nevertheless, there is great heterogeneity among different studies concerning the outcome measures and the number of patients subjected to ART, which is not explicitly stated. Additionally, most studies are lacking information about the obstetrical outcome and complications of pregnancies after OTT. Another concern is the limited follow-up period. Last but not least,

data are sparse on prepubertal girls which are a targeted population for the application of the technique. Prolonged cryopreservation and prepubertal status at retrieval may affect reproductive performance, but no sufficient data exist to test this hypothesis.

CONCLUSIONS

The present review demonstrates the available data on the safety and efficacy of ovarian tissue transplantation in restoring fertility. The findings of this work support the procedural safety of the technique and confirm an acceptable live-birth rate of 32.7%. However, the absence of randomized clinical trials precluded any sound estimation about the safety and efficacy of the technique in comparison with other FP options and this is a potential field of future research. More studies are needed to endorse or discourage wide clinical application.

Disclosure of interest

The authors report no conflict of interest.

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Безопасность и эффективность аутотрансплантации ткани яичника: систематический обзор литературы

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Резюме

Аутотрансплантация ткани яичника — это инновационный метод сохранения фертильности, который спровоцировал продолжающиеся исследования. Цель настоящего исследования состояла в том, чтобы оценить безопасность и репродуктивную функцию аутотрансплантации ткани яичника. Этот обзор проводится в соответствии с рекомендациями PRISMA. Семь исследований соответствовали критериям включения. В общей сложности 3427 пациенток подверглись криоконсервации ткани яичников, 205 – аутотрансплантации. Извлечение ткани в основном выполнялось лапароскопически, и возникло только одно серьёзное осложнение. Трансплантации проводились преимущественно открытым способом, и данных о безопасности было недостаточно. Всего было проанализировано 295 аутотрансплантаций, в результате которых наступило 104 беременности. Шестьдесят пять беременностей привели к живорождению, а девять продолжались на тот момент. Наблюдались частота наступления беременности 50.7% и частота живорождения 32.7%. На естественное зачатие приходилось 46.3% живорождений. Дефицитов при рождении не зарегистрировано. Аутотрансплантация ткани яичника представляется безопасной процедурой с приемлемой частотой наступления беременности.

Ключевые слова

аутологичные, криоконсервация, вспомогательные средства, сохранение фертильности, живорождение, трансплантация, репродуктивные технологии