Best Practice & Research Clinical Obstetrics and Gynaecology 28 (2014) 1188–1197

Contents lists available at ScienceDirect

Best Practice & Research Clinical Obstetrics and Gynaecology

journal homepage: www.elsevier.com/locate/bpobgyn

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Transplantation of ovarian tissue

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Keywords:
ovarian transplantation
pregnancy outcome
complications

Since the first live birth after orthotopic transplantation of frozen–thawed ovarian tissue, >40 babies have been born. It is time to consider fertility preservation in women as one of the foremost challenges of the next decade and to offer women facing the risk of induced or iatrogenic premature menopause the best chances of becoming mothers.

Heterotopic transplantation has also been attempted, with consistent restoration of endocrine function; nonetheless, its clinical value remains questionable as it may not provide an optimal environment for follicular development, possibly because of differences in temperature, pressure, paracrine factors and blood supply.

Finally, orthotopic allo-transplantation of fresh human ovarian tissue has been successfully attempted between monozygotic twins and also between genetically different sisters.

The next step in this field will be the development of an artificial ovary, using, as a support, a biodegradable scaffold made of an alginate matrigel matrix onto which isolated preantral follicles and ovarian cells can be grafted.

Introduction

Significant developments in cancer therapy over recent decades have led to a dramatic improvement in survival rates, and many cancers can now be cured, raising the important issue of subsequent

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http://dx.doi.org/10.1016/j.bpobgyn.2014.09.003
1521-6934/

quality of life [1]. Unfortunately, treatments such as chemotherapy, radiotherapy and/or surgery result in premature ovarian failure (POF) in some instances, robbing these women of the chance of conceiving a child [2–6].

This is particularly pertinent for young women wishing to start a family once in disease remission. Indeed, the number of new cases of invasive cancer in women in the USA was approximately 790,740 in 2012, and around 10% of these cases were in women aged <45 years [7].

Non-malignant systemic diseases like autoimmune and haematological disorders may also require chemotherapy or radiotherapy, often associated with bone marrow transplantation (BMT) [8,9]. Impairment of ovarian function after BMT is generally linked to increased age at the time of treatment and use of total body irradiation prior to transplantation [10,11].

Ovaries are particularly sensitive to cytotoxic drugs, especially alkylating agents, which are likely to lead to gonadal dysfunction [11–14]. Cyclophosphamide is the alkylating agent implicated in causing most damage to oocytes and granulosa cells depending on dose, while a combination of abdominal ionizing radiation and alkylating agents leaves almost 100% of patients infertile [15–17].

Pelvic radiation therapy also causes POF, with exposure levels of 5–10 Gy known to be toxic to oocytes [15]. Indeed, the human oocyte is very sensitive to radiation and as little as <2Gy may be enough to destroy 50% of primordial follicles [12,15].

This review evaluates the techniques and results of ovarian tissue transplantation.

The ovarian reserve

The term *'ovarian reserve'* typically describes the population of primordial follicles in the ovary constituting what has been called the 'true' ovarian reserve [18]. In assisted reproduction, this term refers to the population of small growing follicles, namely small antral follicles detected by vaginal ultrasonography.

Initiation of the resting primordial follicle reserve begins during fetal life, when around 100–2000 primordial germ cells colonize the genital ridges and embark upon a massive proliferation process that culminates in 7×10^6 potential oocytes at mid-gestation, but approximately 85% of these potential oocytes are lost prior to birth [18,19]. The number of follicles continues to decline throughout reproductive life, during which time only ~450 monthly ovulatory cycles occur. Most follicles undergo atresia during the growth phase, involving their degeneration and subsequent resorption. Cyclic folliculogenesis and ovulation, with massive follicular atresia and ageing-induced apoptosis, result in ovarian atrophy and reduced fertility [18–20].

Various mechanisms have been proposed to account for the decline in fertility experienced by women >40 years of age, including poor oocyte quality characterized by abnormalities in the meiotic spindle, shortened telomeres or chromosome misalignment [21,22]. At menopause (occurring on average at 50–51 years of age), some 1000 primordial follicles remain (Fig. 1). While mitotically active germ cells have been documented in mouse and human ovaries [23], their presence and capacity for neo-oogenesis remain contentious [24].

Fertility preservation: different options

Fertility preservation options in cancer patients give these women the opportunity to become mothers when they have overcome their disease. Alternatives include embryo cryopreservation [2], immature or mature oocyte cryopreservation [25] and ovarian tissue cryopreservation (see Ref. [1] for review).

Cryopreservation of ovarian tissue is the only available option for prepubertal girls and women who cannot delay the start of chemotherapy [1,17,26]. The age of the patient should be taken into account, because the follicular reserve of the ovary is age-dependent [5]. It is well documented that fertility becomes compromised during the mid-30s; for this reason, the procedure should probably not be offered to women after the age of 38 years. In many centres, the limit is fixed at 35 years [1,3].