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COMMENTARY

Revisiting the role of heterotopic ovarian transplantation: futility or fertility

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Abstract Scepticism hovers over the future of heterotopic transplantation of cryopreserved human ovarian tissue, as its clinical efficacy and practicability for fertility preservation is still debatable. Despite its limitations, the potential advantages and roles of heterotopic transplantation should not be ignored. Indeed, restoration of ovarian function after heterotopic transplantation of cryopreserved ovarian tissue has been consistently demonstrated in humans. There are many unknowns with this technology, such as the optimal heterotopic site, environmental factors and oocyte quality. Hence, it will require further investigations before making a final verdict. Until then, rather than being considered prematurely as a futile technology, heterotopic ovarian transplantation should be viewed positively, with potential roles for restoration of ovarian function and fertility.

KEYWORDS: cancer, cryopreservation, fertility preservation, heterotopic, ovarian function, transplantation

Introduction

Over the past 25 years, advanced cancer therapy has resulted in a significant decrease in cancer mortality rates (more than 50% reduction) and an increase in cancer survivors as a consequence. Currently, more than 13 million cancer survivors are living in the USA, and approximately 450,000 cancer survivors are of reproductive age. As the number of young cancer survivors expands, it is no surprise to see increase in the demand for fertility preservation before cancer therapy. Indeed, a survey of fertility issues in young cancer patients revealed that fertility after cancer treatment is a major concern (Partridge et al., 2004).

Several strategies for fertility preservation have been developed through application of contemporary cryotechnologies and reproduction technologies, which include the use of gonadotrophin-releasing hormone agonist (GnRHa), cryopreservation of mature oocytes and/or embryos after ovarian stimulation, cryopreservation of immature oocytes or in-vitro maturation (IVM) followed by cryopreservation of metaphase-II oocytes without ovarian stimulation and cryopreservation of ovarian tissue. Of these, cryopreservation of ovarian tissue followed by transplantation has a unique role for fertility preservation in women who require immediate cancer treatment or are contraindicated for ovarian stimulation. This technology is considered to be an investigational procedure at present, as experience with human ovarian transplantation is limited in general and its clinical efficacy is still uncertain. Nevertheless, autotransplantation of cryopreserved ovarian tissue has become a clinically applicable and useful strategy for restoration of fertility since the birth of the first child born as a result of this method in 2004 (Donnez et al., 2004).

Frozen–thawed ovarian tissue can be transplanted either to an orthotopic or heterotopic site. To date, orthotopic autotransplantation of frozen–thawed ovarian tissue has resulted in 24 live births worldwide (Donnez et al., 2013). On the other hand, no baby has been born after heterotopic transplantation (Kim, 2012). Does this mean that it is time to abandon heterotopic transplantation? It is surely a

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debatable topic with many conflicting opinions, but it may be premature to conclude that heterotopic transplantation of cryopreserved ovarian tissue is a futile technology simply because there has been no pregnancy. Since there are insufficient experiences and knowledge on heterotopic ovarian transplantation, especially in humans, I would rather encourage continuing the investigation of heterotopic ovarian transplantation to verify the validity and efficacy of this technology. Indeed, several studies have reported restoration of ovarian function as well as potential fertility after heterotopic transplantation in monkeys and humans (Kim et al., 2009; Lee et al., 2004; Oktay et al., 2004; Rosendahl et al., 2006; Stern et al., 2011; Suzuki et al., 2012). Furthermore, successful induction of puberty after heterotropic transplantation of cryopreserved ovarian tissue has been reported in a 10-year-old girl with severe sickle cell disease (Poirot et al., 2012). These findings are reassuring and support the promise of heterotopic ovarian transplantation, even in light of looming scepticism regarding future clinical applications. Hence, it is worth revisiting the potential roles of heterotopic ovarian transplantation (especially as a strategy for restoration of ovarian function) before abandoning all efforts.

Advantages and limitations of heterotopic ovarian transplantation

The first person who attempted heterotopic human ovarian transplantation was Robert Morris, a professor of surgery at the New York Postgraduate Medical School in the early 20th century. By 1901, he reported a total of 12 cases of auto- and allo-transplantation of ovarian tissue, with three heterotopic autotransplants having restored menstruation for several years (Gosden, 2010). Researchers cannot ignore this historical documentation of ovarian tissue transplantation written more than 100 years ago when trying to rediscover the role of heterotopic transplantation as well as to find the reason for continued research. Although fertility preservation and restoration is the main goal of ovarian tissue transplantation of frozen–thawed human ovarian tissue, now is the time to explore an alternative role for ovarian transplantation, which is restoration and maintenance of ovarian function.

While restoration of fertility by orthotopic ovarian transplantation has been demonstrated in humans, the efficacy and success rates of this procedure are still unknown. It will be necessary to determine the number of transplantation attempts that resulted in live births (as it requires a denominator to assess the success rates and efficacy). In addition, repeated transplantation may be required to achieve a pregnancy as the duration of continued ovarian graft function is limited. When repeated transplantation is required, heterotopic transplantation may be more cost effective and less invasive (reducing surgical complications). Transplantation of ovarian tissue to heterotopic sites can be done even with severe pelvic adhesions that preclude orthotopic transplantation (Table 1). However, one of the disadvantages of heterotopic transplantation is that, unlike with orthotopic transplantation, a natural conception cannot be expected after transplantation of ovarian tissue to heterotopic sites and, therefore, IVF is required for conception (Table 1). On the other hand, the recovery of oocytes from ovarian grafts at the heterotopic site may be easier and convenient. Another advantage of heterotopic transplantation is the ability to closely monitor for the recurrence of malignancy in the graft.

The causes of failed conception after heterotopic ovarian transplantation can be multifactorial and require further investigation. One of concerns is the suboptimal environment of the heterotopic site that may affect follicular development and the quality of oocytes. Indeed, environmental factors at the heterotopic site are not identical to those of the orthotopic site in the pelvis. The conceivable variables include temperature, pressure, space for follicular growth, peritoneal fluid, cytokines, angiogenic factors and the hormonal milieu (Kim et al., 2009).

Optimal heterotopic site

The main cause of follicular loss after ovarian transplantation is ischaemic injury while waiting for angiogenesis to the graft (Yang et al., 2008). The optimal site should therefore be rich in vascularity to facilitate rapid revascularization. Other factors to be considered include ease of transplantation, accessibility for egg retrieval, ample space for follicular development and cosmetic aspects. In particular, the surrounding environment mimicking the appropriate physiological conditions (such as temperature, local pressure, paracrine factors) could be crucial to improve the quality of oocytes developed in the ovarian graft.

Various heterotopic sites have been tested in humans since the time of Robert Morris, including the broad ligament (Gosden, 2010), the rectus muscle (Kim et al., 2004, 2009), forearm (Oktay et al., 2001), breast tissue (Kim et al., 2004), subcutaneous tissue of the abdomen (Oktay et al., 2004) and subperitoneal tissue (Rosendahl et al., 2006; Stern et al., 2011). In primate studies, other heterotopic sites (omentum, the pouch of Douglas, retroperitoneal iliac fossa, uterine serosa, mesosalpinx, and the pelvic wall) have also been tested (Diaz-Garcia et al., 2011; Suzuki et al., 2012). Although intraperitoneal sites such as omentum or subperitoneal tissue appear to be more physiological, the subcutaneous tissue of the abdomen could also provide an adequate environment for follicle growth in both humans and primates (and easy to access). In fact, the successful transplantation of fresh ovarian tissue to subcutaneous tissue of the abdomen of the monkey has resulted in a live birth (Lee et al., 2004).

Although no clinical pregnancy after heterotopic transplantation of frozen–thawed ovarian tissue has been reported in humans, Rosendahl et al. (2006) demonstrated biochemical pregnancy after fertilization of an oocyte retrieved from cryopreserved ovarian tissue grafted to the subperitoneal tissue of the lower abdominal wall. The current study group also succeeded in retrieval and fertilization of multiple oocytes from cryopreserved ovarian tissue transplanted to the space between the rectus sheath and the rectus muscle (Kim et al., 2009). This patient underwent three IVF cycles which resulted in four embryos.

This study centre is comfortable with grafting ovarian tissue to the space above the rectus muscle, as this site is