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ARE WHOLE OVARIAN TRANSPLANTS THE FUTURE OF REPRODUCTIVE TECHNOLOGY?

AS THE FIRST BABY IS BORN AS A RESULT OF WHOLE-OVARY MICROVASCULAR TRANSPLANTATION, IS THIS THE FUTURE OF REPRODUCTIVE TECHNOLOGY, OR SIMPLY A SENSATIONALISING NEWSPAPER HEADLINE?

Sterility in young women caused by premature ovarian failure and cancer treatment is a field explored extensively in reproductive biological research[1]. Whole ovary transplantation has a long history, but only recently have advances led to successful pregnancy in a previously infertile subject. Does this one pregnancy mark the future of reproductive technology? The procedure aims to minimize the follicular loss seen in other techniques, and increase transplanted tissue longevity by rapid revascularization[1,2,4,5], yet studies have shown a disappointing 6% mean post-transplantation follicular survival[2]. Ovarian cortical grafting has shown a remarkable cumulative pregnancy rate of 37% within 12 months[1], but with only one case of human whole ovary transplantation, it is not possible to make a comparable analysis. The future of whole ovarian transplant seems promising, but is currently limited, for example, to between two monozygotic twins, thus further developments are needed, and it is important that other procedures continue to be researched.

Ovarian tissue transplants date back to 1863, with reports of ovarian grafts between rabbits. Research continued successfully in mice and rats throughout the 20th century, but it was thought that the increased complexity of vascular anastomoses in larger species would lead to poor outcomes[3]. This, along with excitement in the wake of in-vitro fertilizaton (IVF) technology drew attention away from the procedure[3]. Methods of enabling fertility preservation, for example in cancer patients, cases of premature ovarian failure and ovarian dysgenesis are currently at the forefront of reproductive biological research[1], and with technological advances and increased professional acceptance, the concept of whole ovary transplantation is being re-explored. Subsequently in November 2008, the first baby was born to a mother who had undergone a whole ovarian transplant. Though hailed as breakthrough in reproductive technology[1], is this the future of fertility treatment?

Whole ovary transplantation is performed via mini-laparotomy, with the donor's ovarian veins and arteries anastomosed with the corresponding blood vessels in the recipient[5]. In this pioneering case the post-menopausal patient received an ovary from her reproductively healthy monozygotic twin. The process took 100 minutes under warm ischaemic conditions, far short of the 4 hours that the ovarian cortex and primordial follicles have been shown to withstand[4]. Ultrasonography showed normal blood flow to the transplanted ovary both immediately and long term, and normal follicular development. On day 101 post-transplant the recipient menstruated and had 11 regular cycles until she became pregnant[5], affirming ovarian transplantation as a valid technique for restoration of ovarian function.

Does whole ovarian transplant have the edge over ovarian cortical grafting?

Ovarian cortical grafting is a rapid procedure involving the removal of the outer 1mm of the ovarian tissue, that which contains the follicles, and subsequent suture to the medulla of a recipients ovary[3nt,5]. It is less invasive than whole ovary transplant, therefore reduced operative risk and recovery time[4]. The process has shown promising results, but the prolonged period of warm ischaemia (3-7 days during revascularization[2]) leads to a characteristic loss of 50+% of primordial follicles and virtually all growth-phase follicles[1,3,5]. In Silber et al's recent study of this procedure menstrual cycles were restored in all 8 cases and a remarkable 71% pregnancy rate was seen. Thus it was concluded that this technique restores ovulatory function robustly[4]. This is substantiated by a 2008 review, which showed that 25 women, who had undergone tissue transplant treatment seeking pregnancy, achieved a cumulative pregnancy rate of 37% within 12 months[1]. The speed of recovery is currently an unknown

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factor, with refractory periods ranging from 65 days up to 9 months[4] before the first menstruation. Graft longevity also seems to be unpredictable, from 739 days upwards[4], but it has been suggested that with whole ovary transplant there may be longer duration of function[4,5]. Further research is needed to conclusively assess whether these differences are due to technical aspects of surgery or patient selection.

Unfortunately, there are no extensive human studies available regarding whole ovary transplantation, and data on cortical grafting is still sparse. In the future a multicenter trial with sufficient follow-up is necessary to enable comparable analysis of procedure success, and highlight long-term effects of both procedures.

Does whole ovarian transplantation have limitations?

Theoretically, whole ovarian transplant should better maintain follicles than alternative methods due to shorter time spent in warm ischemia. This is challenged by Courbiere et al's (2008) study of whole ovarian transplantation versus cortical grafting with ewe ovaries[2] which highlighted a disappointing 6% mean post transplantation follicular survival, potentially disputing this hypothesis, though natural spontaneous conception was seen.

Further limitations include the need for women seeking whole ovary transplant to have a monozygotic twin of normal reproductive health[1,3,4,5]; a fairly rare phenomenon[4]. There is a possibility of ovarian tissue transplant between genetically non-identical sisters, but it is only likely to be successful if the recipient already has good immunological compatibility with a donor, for example after a bone marrow transplant, which again is a rare occurrence[3]. Furthermore, the loss of primordial follicles throughout life makes older donors less preferable due to increased susceptibility to failure from follicular loss[3].

Moreover, as with many fertility treatments, ovarian transplant has been met with ethical controversy; The British Fertility Society only supports treatment for young women who lose their fertility due to illness. Ovarian transplant, if successful in otherwise healthy post menopausal subjects, could potentially prolong a woman's reproductive lifespan to conventionally 'unsuitable' child-bearing age[1], a subject which already causes controversy with IVF.

Are whole ovarian transplants the future of reproductive technology?

Oocyte donation is the current treatment for women suffering with premature ovarian failure, however research into alternatives, such as ovarian cryopreservation is ongoing, but cellular damage due to ice crystals has led to high risk of aneuploidy, and a consequentially low 4.2% clinical pregnancy rate- not yet equivalent to that of fresh grafts[2].

With recent encouraging findings[1,4], its potential as long-term method of overcoming sterility[4] and potential hormonal benefits of restoring full ovarian function, whole ovary transplant warrants further investigation however the lack of a firm favourite in the race to restore ovarian function, where appropriate to do so, means alternatives must also be researched. Future advances in knowledge and technology will benefit this procedure, but currently it cannot be conclusively stated whether whole ovary transplants are the technique for the future.

1. Bedaiwy MA, El-Nashar SA, El Saman AM, Evers JLH, Sandadi S, Desai N and Falcone T (2008) Reproductive outcome after transplantation of ovarian tissue: a systematic review. *Human Reproduction* **23;12**, pp2709–2717

2. Courbiere B, Caquant L, Mazoyer C, Franck M, Lornage J and Salle B (2008) Difficulties improving ovarian functional recovery by microvascular transplantation and whole ovary vitrification. *Fertility and Sterility* [Article in press]

3. Gosden RG (2008) Focus on Fertility Preservation Ovary and uterus transplantation [review]. *Reproduction* **136**, pp671–680

4. Silber SJ, DeRosa M, Pineda J, Lenahan K, Grenia D, Gorman K and Gosden RG (2008) A series of monozygotic twins discordant for ovarian failure: ovary transplantation (cortical versus microvascular) and cryopreservation. *Human Reproduction* Feb, pp1–7

5. Silber SJ, Grudzinskas G and Gosden RG (2008) Successful Pregnancy after Microsurgical Transplantation of an Intact Ovary. *The New England Journal of Medicine* **359** Dec, pp2617- 2618

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Task: You are asked to produce a short (2 sides A4 max) "briefing" article (i.e. a short, up-to-date, readable review article) describing our current understanding of a specific topic of your own choice in ***the area of reproductive biology***. The aim of the article will be to promote awareness and interest in research in a topic of reproductive physiology. The article should concentrate on how **the scientific basis** of the topic area has advanced over the last 3-4 years, *with a particular focus on developments in the last 12 months*. It should indicate current areas of research and controversy.

Choice of the topic: You need to give careful thought to the choice of topic. If it is too broad, there is danger your briefing paper will be too superficial and of little interest. You need to choose a subject area in which recent advances have been made. One of the challenges of this task is to produce a balanced article that allows the reader to understand both the background and the current state of knowledge.

Target audience. Final-year undergraduate students, post-graduates, staff with a general interest in reproductive physiology. The style of the briefings should appeal to both non-specialist and specialist readers. It should be at the "New Scientist" kind of level

A good example is a briefing paper from Science, Fazleabas & Kim (2003): SCIENCE 299 (link: http://www.sciencemag.org/cgi/reprint/299/5605/355.pdf).

Also it is worth looking at an article from the Journal of Cell Biology (link: "Me write pretty one day: how to write a good scientific paper"**)** - you might find this helpful for both the current assignment and in other contexts. While you are not trying to write a scientific paper for this particular assignment, (which is the focus of the article above), it has useful comments re style, layout etc.

General format of Briefing Paper:

- No longer than 2 sides of A4 (including tables, diagrams, references). DO NOT EXCEED THE SPACE ALLOCATION otherwise it will not be marked.
- A brief, self-contained summary (not more than 1/4 of a side of A4) should be given at the start of the article. This should be in **bold font.**
- Clear explanatory diagrams or Tables encouraged where appropriate.
- No more than 5 references should be given, and normally not more than two of these should be a review article. The others should normally be primary scientific papers.
- Work must be typewritten with font size 12 for the main text, with at least 1.5 cm margins all round. Lines can be single spaced.
- **TWO** COPIES MUST BE HANDED IN TO THE ACADEMIC CENTRE BY THE DEADLINE SET. When you hand your work in, please use a paperclip to keep ONE COPY of your 2 page assignment together (we will want to separate the pages for production of a booklet), and staple the other copy. DO NOT put in plastic wallets/ or folders.
- **Each** piece of work must bear **YOUR name and email address** on the top RIGHT HAND CORNER of ***each*** sheet of paper.

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- You are advised to look carefully at the marking scheme for the work so that you can decide how best to meet the criteria.

1. **Citing references: Inaccurate citing of references will lose marks.** You must ensure that all references cited in the text are included in reference list, and vice versa.

1. In a **reference list**, references should be given in alphabetical order. In the case of numbers of papers by the same author, these should be given in the order: (a) single author, (b) two authors alphabetically according to the name of the 2nd author, (c) three or more authors chronologically (a), (b) (c) etc for papers published in the same year. Journal titles should be given in full.

In the reference list, references to papers in journals should be given in the following format:

Larson RC, Ignotz GG and Currie WB (1992) Effect of fibronectin on early development in cows. *Journal of Reproduction and Fertility***96**, 289-297

References to books should include: Chapter title, date, edition, name of publisher, city of publication:

e.g.. Aitken RJ (1983) The zona-free hamster egg penetration test. *Male Infertility.* pp 75-86. Ed TB Hargreave. Springer-Verlag, Berlin.

References for web sites should include the author of the site, date of production of site material, and date site was accessed as below:

Nye, David. 1998. A physician's guide to fibromyalgia syndrome [online]. Available: http://www.muhealth.org/~fibro/fm-md.html [accessed 20.3.00]

2. **Any Tables and Figures** should be numbered and bear a clear, *self-explanatory* legend - i.e. the reader should be able to understand the Figure or Table without reference to the text. All symbols and abbreviations used should be explained in the legend The reference source of all tables, figs. etc should be given where appropriate.

3. **Completion dates**. You are advised that the deadlines set are real deadlines. **Work should be handed in to the Academic Centre where the hand in date/time will be recorded. College policy is that work handed in late will not be marked.** YOU should keep a copy of all pieces of work you produce as your originals may not be handed back to you as they may be required for the examiners.

Title
Layout
Summary
Factual content
Logical
Clarity of expression
Stimulating reader interest
Use and clarity of Figs/tables
Correct citing of references

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To get a 1st = Well written, clear, logical, organised, accurate and interesting article showing an excellent understanding of the topic area and stimulating readers interest. Evidence of critical evaluation and understanding demonstrated by selection and presentation of material. No use of undefined or unexplained terms or serious omissions. Up-to-date.High scientific standard.