The Royal Children's Hospital Fertility Preservation Service
Ovarian Tissue Cryopreservation (OTCP) Information Sheet for Leukaemia Patients

Impact of Treatment on Fertility

Some cancer treatments affect fertility. Children and adolescents who receive treatment for Leukaemia receive medication called alkylators which are known to affect fertility. Treatment can affect the number of eggs and follicles (containing immature eggs) in the ovary. The risk to fertility can be low, medium or high risk, depending on many factors including the dose of treatment received, age and gender.

For a young biological female who has not reached puberty, we believe the risk to fertility becomes moderate after receiving ≥8g/m2 of cyclophosphamide, and high after receiving ≥12g/m2. The impact on the ovary increases with age, so for a teenager who has gone through puberty, the risk to fertility becomes moderate after receiving ≥4g/m2 of cyclophosphamide and high after receiving ≥8 g/m2. Unfortunately, we can't be exact about these risk estimates due to insufficient data.

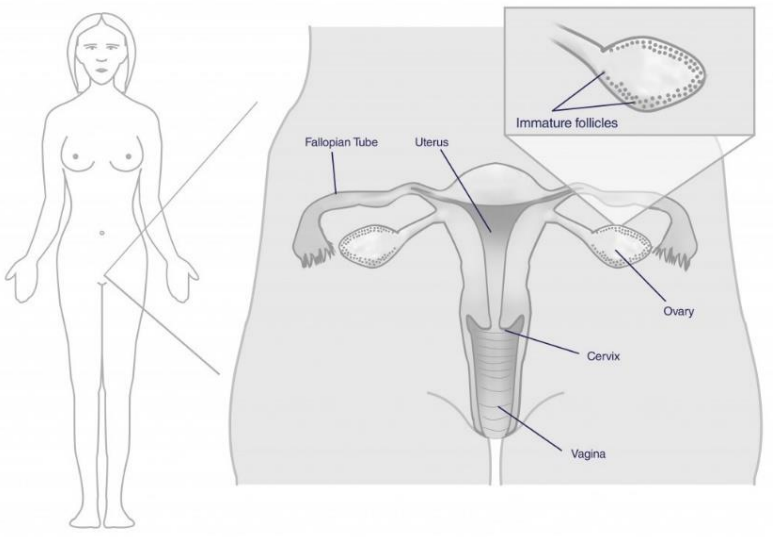
To many parents and young people, fertility is important to them, and many people ask about ways that fertility could potentially be protected.

What Is Fertility Preservation?

Fertility preservation is a process that aims to give patients the opportunity to freeze sperm, eggs or reproductive tissue. It is hoped that this may protect a person's ability to have a biological child in the future. Some of these procedures are proven to assist fertility with live births recorded, and others are considered experimental.

Reproductive System in Biological Females

When a biological female is born, the ovaries will contain hundreds of thousands of immature eggs (follicles). These are all the eggs required for life and they stay inactive until puberty. When puberty begins, usually between the ages of 8 & 14, the pituitary gland (located near the brain) starts making hormones that stimulate the ovaries to make hormones such as Oestrogen. Oestrogen causes breast development, and periods. About once a month, during ovulation in adults, an ovary sends a tiny egg into one of the fallopian tubes. Unless the egg is fertilised by a sperm, a period occurs 2 weeks later.



Ovarian Tissue Cryopreservation (OTCP) – what is it?
OTCP involves the collection of healthy ovarian tissue, often, prior to starting treatment that may harm the ovaries. The tissue contains immature follicles. It is then preserved and frozen until your child is ready to think about starting a family.

This procedure is not routinely undertaken for those at low risk for infertility unless there are special circumstances. This is because:

1. It is an innovative procedure. It is important to understand that there is no guarantee that the freezing of ovarian tissue will lead to successful pregnancies and/or live births. Approximately 200 births have been reported worldwide using ovarian tissue cryopreservation technology. Three live births have been reported in women who have had their tissue stored in childhood.
2. Furthermore, in someone receiving only low risk treatment, we would hope that there are other options for protecting fertility down the track. For example, collecting mature eggs later in life.
3. Sometimes people are too sick at the start of cancer treatment. In this situation, urgent chemotherapy without any delays can be lifesaving.
4. The surgery (Laparoscopy, OTCP, removal of one ovary) is not experimental as this procedure is performed routinely by Gynaecologists and surgeons for other indications. But it does have risks. These include:
    - Risk of a general anaesthetic
    - Infection
    - Bleeding
    - Damage to internal structures (bladder, bowel, blood vessels) which may occasionally require performing an open operation. These risks are likely to be higher during cancer therapy
    - Risk of changing from keyhole surgery to a larger incision (laparotomy)

Special Considerations
For patients with Leukaemia there are special considerations. There are only two ways to try and use the tissue.

- One way is to implant the tissue back into the body in the hope that it will produce eggs. Unfortunately, tissue that has been collected from patients who have been diagnosed with Leukaemia, are not able to have this tissue reimplanted due to the risk of malignant cells being present and reintroducing Leukaemia back into the body.
- Another way is to try to mature the tissue outside the body in an IVF lab via a process called In-Vitro Maturation (IVM). In this scenario, we try to mature the eggs outside the body in the IVF lab. In the future, the eggs could potentially be fertilised with sperm and the resulting embryo would be transferred into the uterus. However, IVM is under development and in the very early phases of research, therefore it is currently considered an experimental technique

Who is Eligible for OTCP?
Theoretically, there is no lower age limit for OTCP and it can be offered to patients of all ages. However, your child needs to be well enough for surgery. Multiple abdominal scars, bleeding disorders or serious immune deficiency may preclude your child from having the procedure done.

In a very young child, the ovaries will usually be very small and it is highly possible that one entire ovary may need to be removed. We cannot guarantee that the ovarian tissue collected or the remaining ovary will be functional in the future.

What Other Options Are Available?

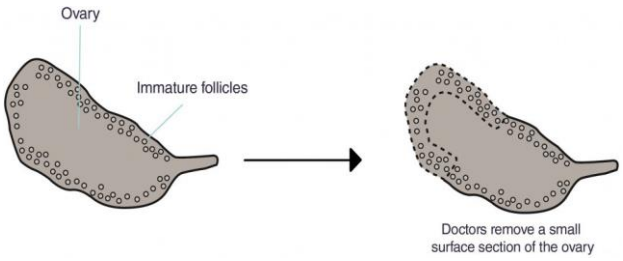
- Your child can have their ovarian function assessed later after treatment in follow-up clinic.
- Egg donation from mother, sister, female relative or other donor in the future.
- Fostering or adoption.
- For post pubertal females, there is the option to have an injection called Zoladex® which is a hormone that suppresses ovarian function and may protect the ovary. Studies in adult women

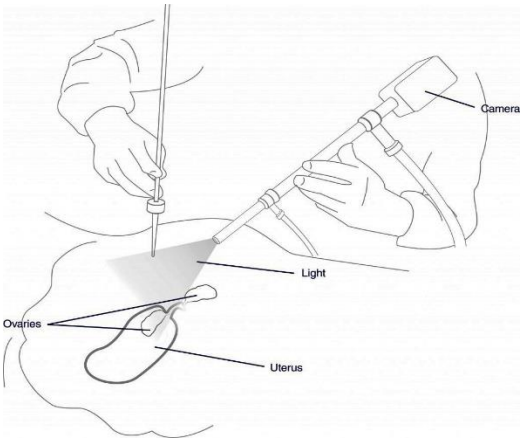
suggest that Zoladex® may have a small protective effect on fertility, but there are no studies in teenagers. Zoladex® is also used to suppress menstruation during chemotherapy.

- If the situation changes and the doses of treatment will become moderate or high risk to infertility, and surgery is deemed safe, then OTCP may be considered at a later date.

What Does OTCP Surgery Involve?

The procedure is performed via laparoscopy (also known as 'keyhole' surgery), which involves a small incision in the belly button, along with 2-3 other small incisions in the abdomen, through which a camera and other surgical instruments are inserted. The surgeon will assess the ovary and then remove about 1/2 to one ovary. The whole ovary is removed if it is very small, or if the treatment is likely to cause a severe impact on future ovarian function. The procedure takes approximately 30 minutes and is usually coordinated with another procedure. Each of the incision sites will have a small dressing on them and recovery time is usually a few days.





Currently, scientists from the Reproductive Services Unit at The Royal Women's Hospital (RWH) collect the tissue from theatre and process it at their centre. A small piece is tested for quality assurance to check for infections and malignant cells in the tissue. The remainder is sliced, placed in liquid and frozen until required for future fertility treatment.

Other Issues to Consider

- Cost of tissue storage: currently the RWH does not charge for the storage of tissue until your child turns 21. After this, there will be an annual storage fee.
- Cost of IVF treatment if required.
- The tissue may be stored at an alternate IVF centre: there may be storage and transport costs involved.
- The tissue can only be used by your child. In the unfortunate event of the death of your child, the tissue cannot be donated to research or be utilised by anyone other than your child. Therefore, the tissue must be either:
  - Disposed of
  - Released to a nominated funeral director for burial/cremation with your child

Who Do I Contact For Further Information?

For further information, please contact the Oncofertility team at RCH.

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