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Mickey might want kids one day

Information for boys and young men with cancer, their parents, carers and doctors.

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Fertility in boys after chemo and radiotherapy

Dear Patient,

Cancer and treatments like chemotherapy, radiotherapy and surgery can have a negative effect on the development of your fertility. You probably aren't thinking about whether you'll be able to have children at the moment, but it may be something that's important to you in the future. This booklet gives you important information about fertility.

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What does fertility mean for a man?

A man's fertility is his ability to have children of his own. It begins with puberty and reduces as he gets older, although men can often have children at quite a late age.



How do chemo and radiotherapy work?

Chemotherapy is a treatment that uses medicines to stop or slow down cell division. The medicines particularly target cells that divide quickly. It's mostly the malignant or harmful cells that are destroyed by chemo to cure the cancer. But some chemo drugs also destroy sperm cells and the early cell forms that will later become sperm cells.

Radiotherapy can also destroy healthy cells, like sperm, that are in the part of your body exposed to the radiotherapy treatment. Sperm production is particularly sensitive to this, but production of the sex hormone testosterone, which also takes place in the testicles, can be affected too. Radiotherapy to the pelvis, or radiotherapy of the head can affect fertility. This is because the production of sex hormones in the testicles depends on the production of sex hormones in the brain.

So chemo and radiotherapy can both lead to a loss of fertility. But we cannot always tell how high the risk is for a particular person. Latest research estimates that up to a third (33 %) of boys and teenagers can become infertile after chemo or radiotherapy. That compares to just 5-10% for the whole population.

You can find more information about the likelihood of reduced fertility and the risk factors at:
https://kinderonkologie.charite.de/forschung/ag_borgmann_staudt/

How do sperm cells mature and why are sex hormones important?

The testicles contain lots of little tubes, called seminiferous tubules, where sperm cells are made (see diagram 1). When puberty begins, the stem cells in the testicles develop into mature sperm, under the influence of sex hormones. This is a continuous process inside the testicles, and it takes about 10 weeks for new sperm cells to develop. The sperm are first stored in ducts leading from the testicles. During ejaculation they move from here to come out of the body from the penis. In a fertile man, one milliliter (ml) of semen contains at least 39 million sperm and he will ejaculate at least 1.5 ml of semen at a time.

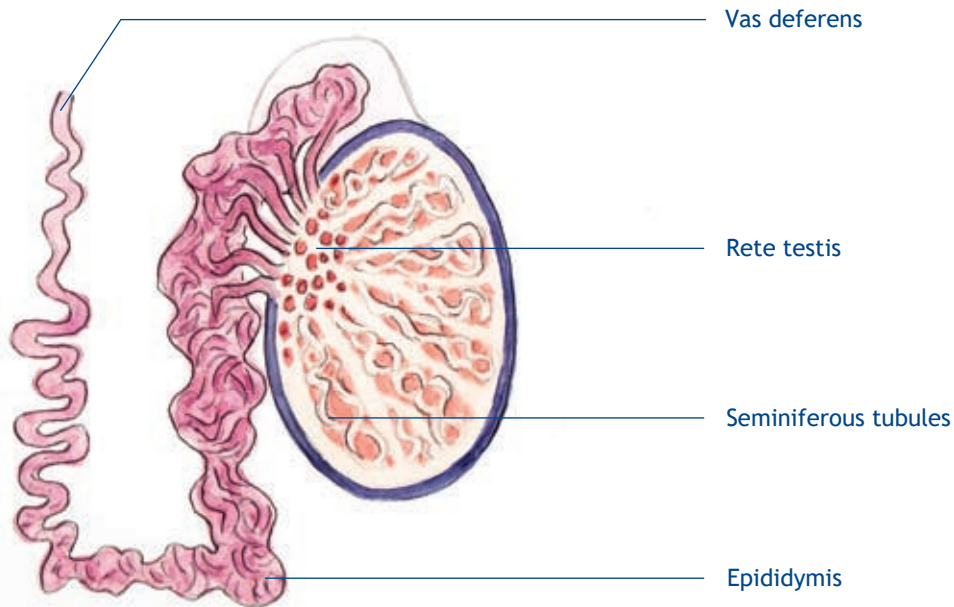
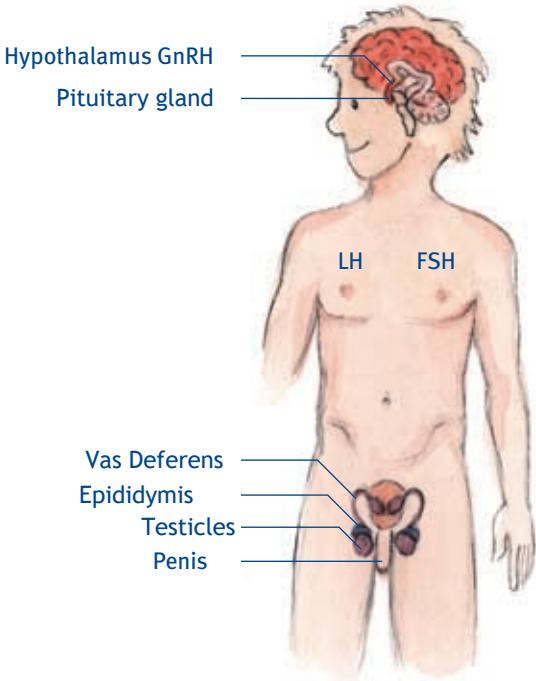
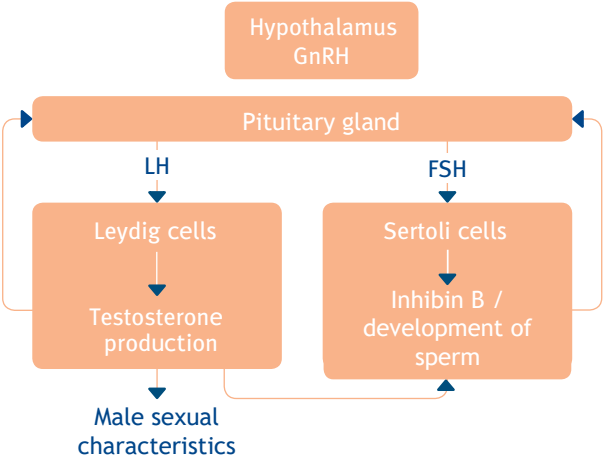


Figure 1 shows a cross section of a testicle, with the epididymis and the vas deferens.

A gland in the brain, called the hypothalamus, produces the hormone GnRH which makes sperm cells mature and allows the sexual organs to develop. GnRH stimulates another part of the brain, the pituitary gland, to produce two other hormones, FSH and LH. These two hormones travel from the pituitary gland to the testicles where they stimulate the Sertoli cells to produce sperm and the Leydig cells to produce testosterone. The male hormone testosterone causes the male sexual organs to develop and male characteristics to appear, like a deep voice, body hair and muscles. The Sertoli cells also produce the hormone inhibin B, which regulates the release of FSH. So inhibin B is also responsible for the development of sperm cells.



Figures 2 and 3:
The cycle of sex hormones and relevant organs

How does a sperm fertilise an egg?

Sperm can live for two or three days inside a woman's vagina, womb or fallopian tube. Unfertilised eggs survive only 12 hours. Fertilisation usually takes place in the fallopian tube (figure 4).



The chance of getting pregnant for a healthy, young couple is about 20 % per menstrual cycle. That means that a couple needs on average five months (five menstrual cycles) for the woman to get pregnant. If a couple has been trying to get pregnant for two years without success, we talk about infertility.

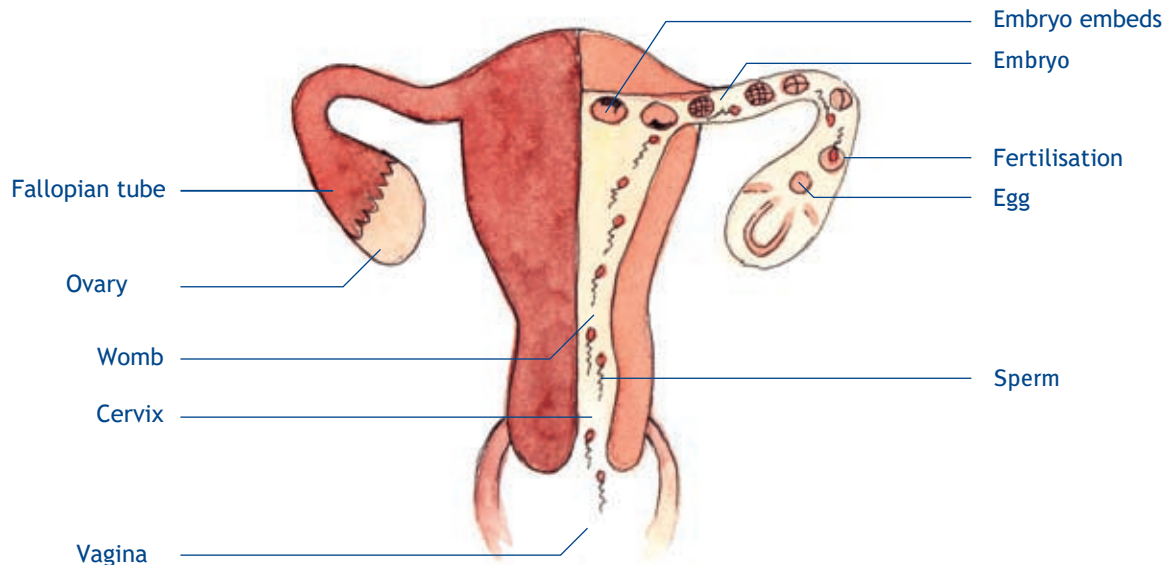


Figure 4 shows the sperms' path to fertilising an egg

What are the risk factors for reduced fertility?

Scientists have been researching the risk factors for reduced fertility after cancer treatment for many years. But because treatment has several components, and each person responds differently to the different drugs, it's hard to tell for sure, which element of the treatment affects fertility at which dose. The risk factors that follow are what we know from the present state of research, and will continue to be tested. By looking at sexual characteristics, like the growth of pubic hair and size of the testicles, and through hormone tests, we can estimate a young person's individual fertility. This is particularly advisable if your treatment started after puberty and if you had one of the treatments below, as this puts you at high risk of reduced fertility.

- Radiotherapy of the pelvis of around 4 Gray or more, if the pelvic area is affected by cancer
- Whole body radiotherapy (total body irradiation) of around 4 Gray or more, previous to a stem cell transplant
- Procarbazine from about 6 g/m², or less, in the case of Hodgkin's lymphoma

There are some other chemotherapy drugs that are sometimes used in the treatment of childhood cancers that can harm fertility in certain doses. You'll find a list of them in the appendix on page 20.

Get your doctor to fill in below what treatments you've had and whether they have a low, medium or high risk of affecting your fertility.

Treatment: _____

with: high risk medium risk low risk

You'll find more information about the GPOH Society's therapy protocols at: www.kinderkrebsinfo.de

How can my fertility be assessed?

A basic examination to assess fertility usually involves:

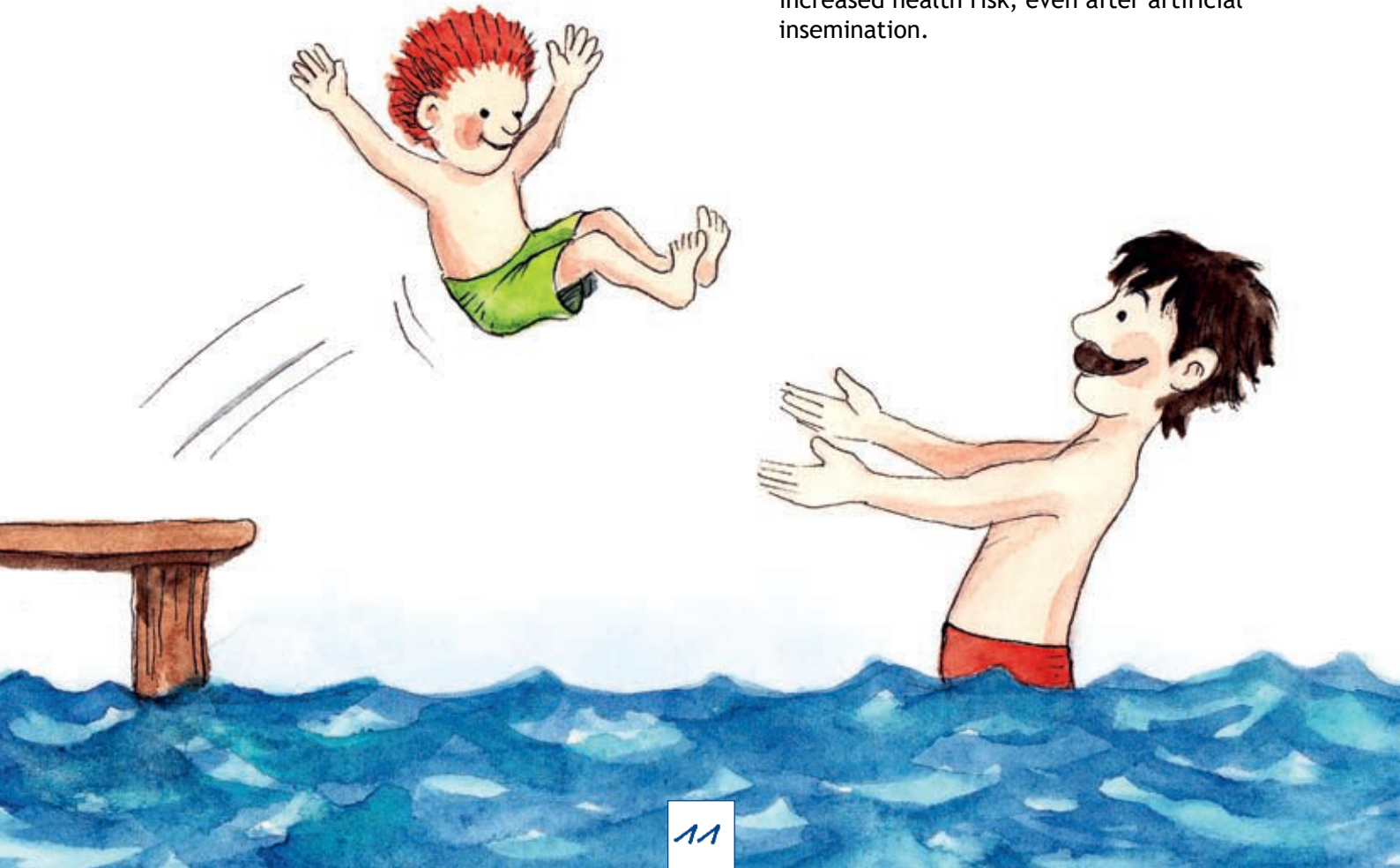
- a medical history
- a physical examination: if you have little or no facial hair, limited pubic hair and your voice has not broken, this would suggest too little testosterone. Testicles in young men that are smaller in volume than 12 ml (3 x 2 x 2 cm) also indicate that fertility could be affected.
- Hormone tests:
This involves measuring the levels of sex hormones LH, FSH, testosterone and inhibin B in your blood. It will be important to know at the time the blood sample is taken and whether you have taken any sex hormones, as these will affect the test results and how they are judged. An abnormal result will have to be confirmed by at least one more test, as hormone levels can vary.



We can also do a semen analysis, to assess your fertility more accurately. If the result is abnormal, it should be confirmed by a repeat test at least 10 weeks later. If the repeat test confirms no live sperm in the semen, we can do a biopsy of the testicles and often get individual live sperm that can be used for artificial fertilisation (fertilising an egg outside the body). In some cases, sperm production can recover a few years after chemo or radiotherapy.

Will my child be healthy?

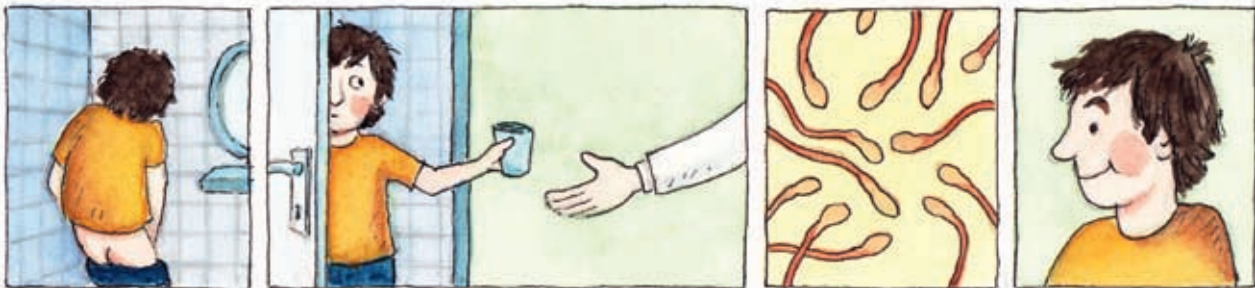
Many cancer patients worry that their children could get cancer too. But lots of research studies, involving thousands of people in Europe and the USA, have shown that the children of people who have had cancer are at no greater risk of either birth defects or of getting cancer themselves. We are currently observing the health of these children across Europe and again find no increased health risk, even after artificial insemination.



What can be done to preserve fertility before and after cancer treatment?

During or after puberty

At the onset of puberty, as soon as your testicles start working and producing sperm, your sperm can be frozen and stored for years. This could be from about the age of 13, when external sexual characteristics have started to develop - so the testicles have grown to a volume of 8 ml and pubic hair has appeared. The easiest way to get sperm is by taking it from semen. You can produce semen by stimulating your penis with your hands (masturbating) (see picture 5). This poses no risk to your health, so is worth considering before treatment, even if the chemo or radiotherapy you are about to have carries only a low risk of harming your fertility. If there are no useable sperm in your semen, you can have a short procedure under anaesthetic to take a sample of tissue from your testicle. The sperm from this sample can then be frozen.



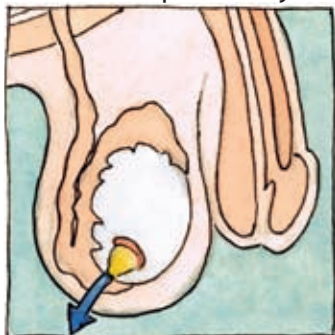
Picture 5 shows how sperm can be taken from semen

If you want to have a child after you have recovered, and your partner doesn't get pregnant naturally, your sperm can be thawed and used for artificial fertilisation. This results in a successful pregnancy in more than half of all cases.

Before puberty

The body only starts producing sperm that can be frozen, after the onset of puberty. But it is still possible to do a biopsy of the testicles before chemo or radiotherapy treatment. This involves a short operation, under anaesthetic, to remove tissue from the testicle, which is then frozen. In this way, the stem cells inside the sample can be preserved for potential development into mature sperm, after you've recovered from your illness. Do be aware, though, especially if you have leukaemia or non-Hodgkin's lymphoma, we can't rule out the possibility that there will be malignant cells in your testicles. In this case, instead of transplanting the tissue sample, we would consider using individual sperm, that have been brought to maturity. The methods for getting sperm to develop in this way are still experimental, so this can only be done in particular hospitals, as part of a research programme.

You can decide with your parents and after consulting your doctor, whether to go ahead with measures to preserve your fertility.



Picture 6 shows a biopsy of the testicle. The doctor conducts a short operation, under anaesthetic, to remove a small piece of the testicle.



What does hormone replacement therapy involve ?

If you have surgery or radiotherapy on your testicles, of a dose higher than 20 Gray, the Leydig cells, which produce testosterone, may be removed or damaged. Testosterone has a significant effect on your sex life, muscle development, bone structure and also on your general wellbeing. If you have too little testosterone after treatment, you can take replacement hormones. These come as a long-working injection, a skin patch or as a gel that is rubbed into the skin.

Radiotherapy of the head, particularly of the hypothalamus (part of the midbrain) and the pituitary gland, of more than 30 Gray, can lead to a drop in production of the hormones LH and FSH. That reduces stimulation of the testicles and causes fewer or no sperm to be produced. But it doesn't have to cause permanent damage to sperm production. In boys before puberty, the testicles should be stimulated with LH and FSH until sperm production begins. When he reaches puberty, he can have testosterone replacement therapy until he wants children, as treating someone with LH and FSH is complicated and expensive.

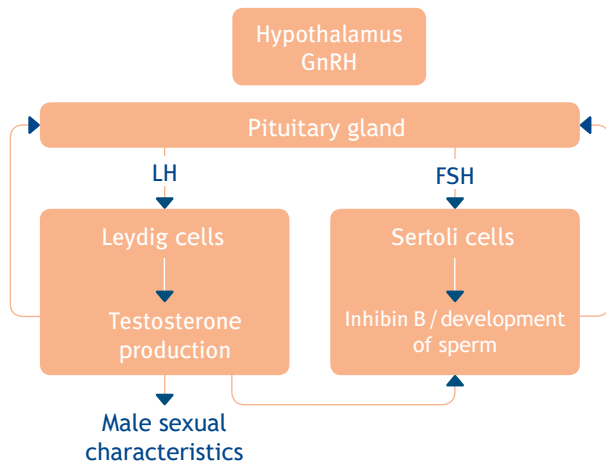
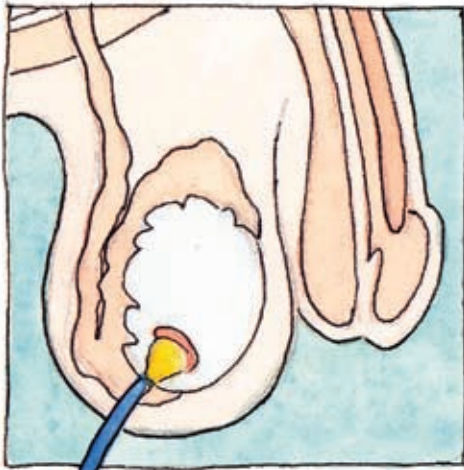


Figure 2: The cycle of sex hormones and relevant organs.

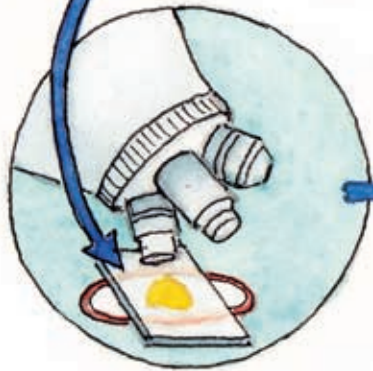
What forms of artificial fertilisation are there?

Artificial fertilisation is only used when a pregnancy can't be achieved through natural methods. How this is best done will depend mainly on the number of eggs that are available. Artificial fertilisation means fertilising an egg artificially with a man's sperm. There are three possibilities:

- The sperm cells are inserted into the woman's womb with the help of a small tube (insemination).
- Sperm are added to eggs in a test tube. Fertilised eggs are then placed in the womb. This is called in vitro fertilization or IVF.
- A single sperm is directly inserted into a single egg. The fertilised egg is then placed into the womb (figure 7, intracytoplasmic sperm injection, ICSI).



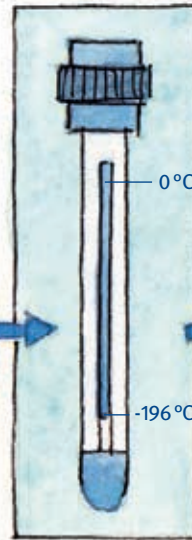
Removing tissue from the testicle, if there are no sperm in the semen



Examining the tissue under a microscope



Sperm in the tissue



Sperm are frozen



ICSI: Sperm are extracted from the thawed tissue and a single sperm is placed inside a single egg

Figure 7 shows the stages of artificial fertilisation, when a single egg is fertilised with a single sperm, after a sample of testicle tissue has been frozen and thawed.

Even when semen repeatedly fails to contain live sperm after chemo or radiotherapy treatment, single live sperm can often be extracted through a biopsy of the testicle, and used for artificial fertilisation.

You can find more information about fertility after cancer therapy on the website www.fertiprotekt.de and also at www.androprotect.de. Here you can also find addresses of experts in your area who can diagnose and treat fertility problems that may occur after chemotherapy or radiotherapy.



Adopting

If you want to become a father, you can also adopt a child. If you would like to adopt a child in Germany, the age difference between the child and the parents should not exceed 40 years. The standards for international adoptions are different, and therefore, parents can sometimes be older.

For example, in Berlin there is a central contact point of Caritas, which would be responsible for you if you want to adopt a child. You can find information about this at:

<https://www.berlin.de/sen/jugend/familie-und-kinder/adoption/> and <https://www.pflege-adoption.de/pflegefamilien>.

For the Berlin region, the Central Adoption Agency Berlin-Brandenburg (ZABB) is in charge. You can find information here:

<https://mbjs.brandenburg.de/kinder-und-jugend/adoption.html>

You can find nationwide information, for example, under the following web links:

- *Federal Centre for Intercountry Adoption:*
www.bundesjustizamt.de/
- *Bundesverband der Pflege- und Adoptivfamilien e. V.:* www.pfad-bv.de/



Psychosocial counseling regarding family planning:

Regardless of whether or on which path you become a father - each path has its own ups and downs, and if you need support along the way, the state cancer societies, for example, are available to you locally. One of their main tasks is to provide psychosocial help and counseling in a total of 124 counseling centres throughout Germany:

<https://www.krebsgesellschaft.de/landeskrebsgesellschaften.html>

DKG
KREBSGESELLSCHAFT

Appendix

The costs of fertility treatment Something to discuss with your parents

The cost of collecting sperm and freezing is about 200 to 400 euros. The storage of sperm cells costs 150 to 300 euros per year. It is recommended to have hormone analyses and/or sperm cell analyses performed at certain time intervals in order to check fertility and to continue or end the storage of frozen sperm cells.

The following costs may be added for future artificial insemination: The medication for hormone treatment of the ovaries (approx. 1,500 to 3,000 euros), the treatment costs for hormone treatment and collection of the eggs (max. 500 euros), the costs for fertilisation of the eggs in a test tube (max. 500 euros) or, if there are few available sperm cells, by direct insertion of a sperm cell into an egg cell (max. 1,500 euros). As of 2021, the costs of freezing eggs and sperm and the associated measures in the context of fertility-damaging treatment will be covered for German health insurance beneficiaries. In individual cases, it is worth asking the local support association for support.

The approximate costs for the collection, freezing and storage of the storage of sperm and for artificial insemination can also be found at www.fertiprotekt.de.
Information on the freezing of pre-pubertal testicular tissue can be found at: www.androprotect.de.



Therapy protocols, particularly for your doctor

Not all chemotherapy drugs are as dangerous to your fertility as others. On page 9, you will find treatments with a high risk (greater than 66% chance) for fertility problems (red box). On pages 20 and 21, we present the drugs and protocols that are associated with a medium risk (greater than 33% chance) (yellow boxes) and a low risk (less than 33% chance) (green box), respectively.

Patients with the following intermediate risk are also recommended to have their fertility evaluated after therapy:

- **CWS-SoTiSaR:** RMS Subgroup C1, D-H; Other „RMS-like“, „Non-RMS-like“ in HR, Metastatic STS; **CWS 02:** SR B, HR; **96:** SR, HR; **91:** SR, HR HR; **86; 81:**
- **EURAMOS-1:** MAPIE; **COSS 96:** HR; **91:** IOR; **86:** LRV-VI, HR
- **Ewing 2008; Euro EWING 99; EICESS 92; CESS 86; 81:**
- **HB 1999:** HB III SD/PD, IV PR; HCC: III / IV PR
- **EuroNET-PHL-C1:** TG2 + 3 random 07–11; **HD 95:** TG2; **90:** TG2; **82:** TG1
- **HIT 2000:** HIT2000-AB4, HIT2000-BIS4-RT; MET-HIT2000-BIS4 CR/PR, PHIT2000-AB4, P-HIT2000-BIS4-RT; E-HIT2000-AB4, E-HIT2000-BIS4-RT
- **NB 2004:** MR <6M, HR; **97:** HR + Mega, HR + DT <6M; **90:** RG2 + 3 A/B-CR, RG3 CD + 4; **82:** III + LK, IV
- **SIOP LGG 2004:** Standard / Intensified Induction; **96**
- **SIOP 2001/GPOH:** II–IV + HR; **93–01:** I–V + HR, IV Non-CR

Medicines that have a medium risk of affecting fertility:

Busulfan ($\geq 0.5 \text{ g/m}^2$), Carboplatin ($\geq 2 \text{ g/m}^2$), Cisplatin ($\geq 0.5 \text{ g/m}^2$), Cyclophosphamid ($\geq 10 \text{ g/m}^2$), Etoposid ($\geq 5 \text{ g/m}^2$), Ifosfamid ($\geq 42 \text{ g/m}^2$), Melphalan ($\geq 0.14 - 0.24 \text{ g/m}^2$), Procarbazine ($\geq 3 \text{ g/m}^2$)

We recommend an examination to assess fertility for patients who've had the following low-risk treatments, only if there are indications that fertility may have been affected.

- AIEOP-BFM ALL 2009, ALL-BFM 2000, 95, 90, 86, 83, 81, 79, 77
- AML-BFM 2004, 02, 98, 93, 87, 83, 78
- Co-ALL-08-09, 03, 97, 92, 89, 85, 82, 80
- CWS-SoTiSaR 2009: RMS Subgroup A, B, C2; 02: LR, SR A; 96: LR; 91: LR, HR LR
- EURAMOS-1: MAP, MAPifn; COSS 96: LR, S1, S2; 91: COSS, COSS/IOR; 90; 89; 86 LR I-IV; 85; 82; 80; 77
- EuroNET-PHL-C1 2007-2011 TG1, TG2 + 3 random, since 2012 TG1-3; EuroNETPHL-LP1; HD 2002 Pilot; HD 95: TG1; 90: TG1; 87; 85
- HB 99: I + II; III PR; HCC: I/II; III/IV PR operable; SD/PD; PR (operable, SD/PD); 94; 89
- HIT-GBM D, C, B, A
- HIT-HGG 2007
- HIT 2000: HIT2000-BIS4 + RT; MET-HIT2000-BIS4 SD/PD, MET-HIT2000-AB4; PHIT2000-BIS4 + RT; E-HIT2000-BIS4 + RT; HIT-MED 99; HIT-SKK 92; HIT 91; 89; 88; HIT-SKK 87
- Craniopharyngeoma 2007, 2000; HIT-Endo 99, 96
- NB 2004: Observation, MR N 6M; 97: SR, HR + DT N 6M; 90: RG2 + 3 A/B + CR, RGS-C 85; 82: II-II, III-LK; 79
- NHL-BFM Registry 2012, B-NHL BFM 04, NHL-BFM 95, 90, 86, 83, 81, 79, 77, 76, 75
- MAHO 98; 94; 92; 88; 82
- MAKEI 96; 89; 86; 83
- SIOP 2001/GPOH: I, II-IV without HR; 93-01 I-V without HR; 89; 82; 80; 79

Radiotherapy of the head of more than 30 Gray in the region of the hypothalamus and the pituitary gland can disrupt testicular production, by reducing production of GnRH or FSH/LH. In these cases, it's worth considering hormone replacement therapy.



Acknowledgements

We would like to thank all the affected families whose cooperation has enabled us to collect this data. We thank our colleagues from the FeCt team for many years of fruitful cooperation, Helmut Schmidt for creating the video, Simon Michael for its musical accompaniment and Dieter Schmitz for the beautiful pictures and the permission to animate them for our second edition.

Berlin, December 2020, © Anja Borgmann-Staudt, Greta Sommerhäuser and Lucía Alacán Friedrich



Impressum

“Mickey might want kids one day”

An informational brochure with video for adolescent male patients with cancer

Publisher 1st edition: Berliner Krebsgesellschaft e. V.

1st edition 2013

2nd edition 2021

Illustration: Dieter Schmitz

Typesetting: da vinci
design GmbH

Printing 1. Auflage:

Wunderlich Dorette Pink

Page



Idea for text and video © Anja Borgmann-Staudt, FeCt working group, in collaboration with members of the FertiPROTEKT, PanCare and the Therapy Optimization Studies networks of the Society for Pediatric Oncology and Hematology. Video realization Helmut Schmidt, coordinator film and shooting Charité CFM Berlin

