

Lucy might want kids one day

Information for girls with cancer, their parents, carers and doctors.

Lucy might want kids one day

An information brochure

for adolescent female patients with cancer - also for parents and doctors





Fertility in girls after chemo and radiotherapy

Dear Patient,

Cancer and treatments like chemotherapy, radiotherapy and surgery can affect 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 in a girl or woman?

A woman's fertility is her ability to have children of her own. It begins with puberty and reduces as she gets older, ending with the menopause. The average age of menopause is 52, but anywhere between 40 and 55 is considered normal.



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 eggs and the early cell forms that will later become eggs.

Radiotherapy can also destroy healthy cells, like eggs, that are in the part of your body exposed to the radiotherapy treatment. A young woman has more eggs in her ovaries than an older woman and the more eggs there are, the greater the chance that some of them will be OK and the woman will stay fertile. Girls who haven't reached puberty are at lower risk of losing their fertility, because their ovaries are not yet active. If the womb is in the path of the rays it can lose its elasticity and its ability to provide nourishment, which could result in a premature (early) birth, or a baby with a low birth weight.

Radiotherapy to the pelvis, or radiotherapy of the head can affect fertility. This is because the production of sex hormones in the ovaries is dependent 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 children 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 eggs mature and why are sex hormones important?

A girl is born with 1-2 million eggs in her ovaries. Each egg cell is surrounded by a covering and together they are known as an ovarian follicle. The body can't produce new ovarian follicles, once they've been destroyed by chemo or radiotherapy. Between puberty and the menopause, sex hormones will cause some of the follicles to mature and, once a month, to release an egg (ovulation). The egg's covering, called the corpus luteum or yellow body, is left behind.

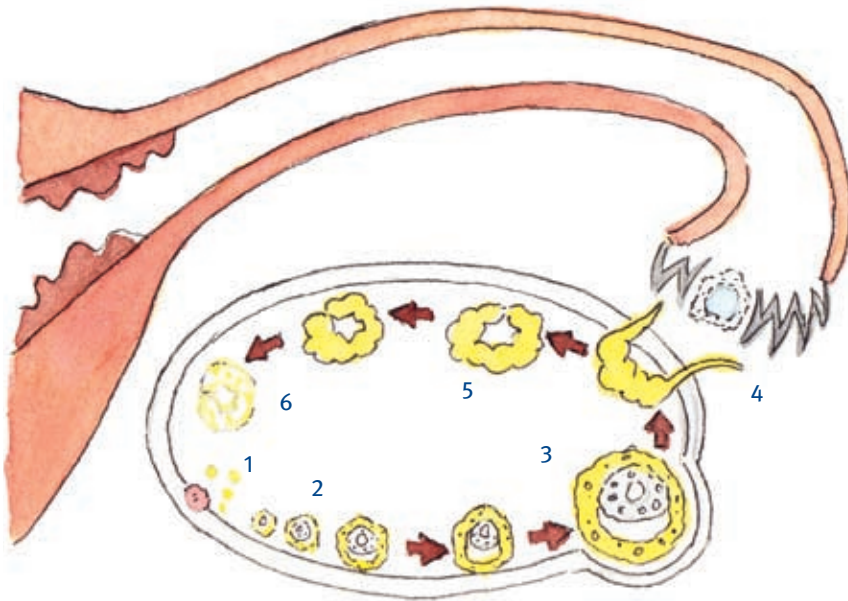
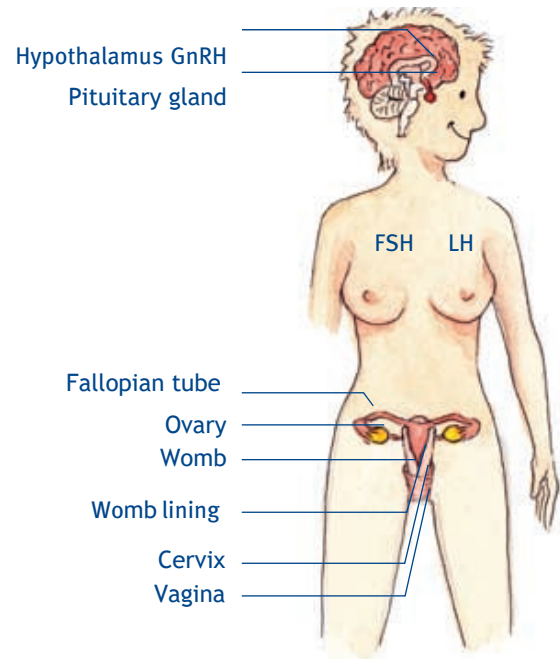
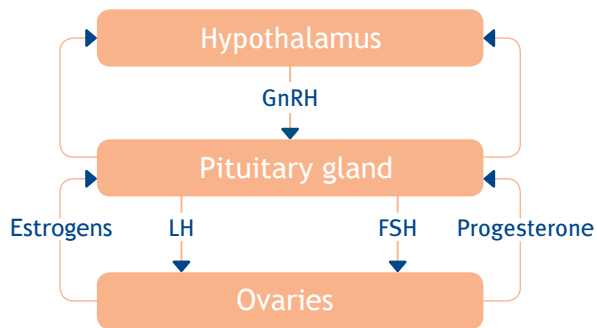


Figure 1: cross section of a fallopian tube and an ovary, showing the development of a follicle, from an egg (1), through ovulation (4) into a yellow body (6).

Follicles mature in the ovaries under the influence of sex hormones. A gland in the brain, called the hypothalamus, produces a hormone known as GnRH. This then causes two other sex hormones, FSH and LH, to be produced in the brain by the pituitary gland (Figures 2 and 3). The two hormones FSH and LH make the follicles in the ovary mature. As they develop, the follicles produce the hormone oestrogen. One of the things oestrogen does is cause the lining of the womb to thicken.

A woman's body goes through a process called the menstrual cycle every four weeks. The cycle starts with the first day of her period (monthly bleeding). In the middle of the cycle, around day 14, ovulation occurs. This is when the ovary releases an egg. The remainder of the burst follicle produces the yellow body hormone Progesterone, which causes the lining of the womb to thicken further. After ovulation, the egg takes about five days to travel down the fallopian tube to the womb. If the egg is fertilised during this time, it settles into the womb lining. If it hasn't been fertilised, the woman starts her period as normal. A new cycle begins.



*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.

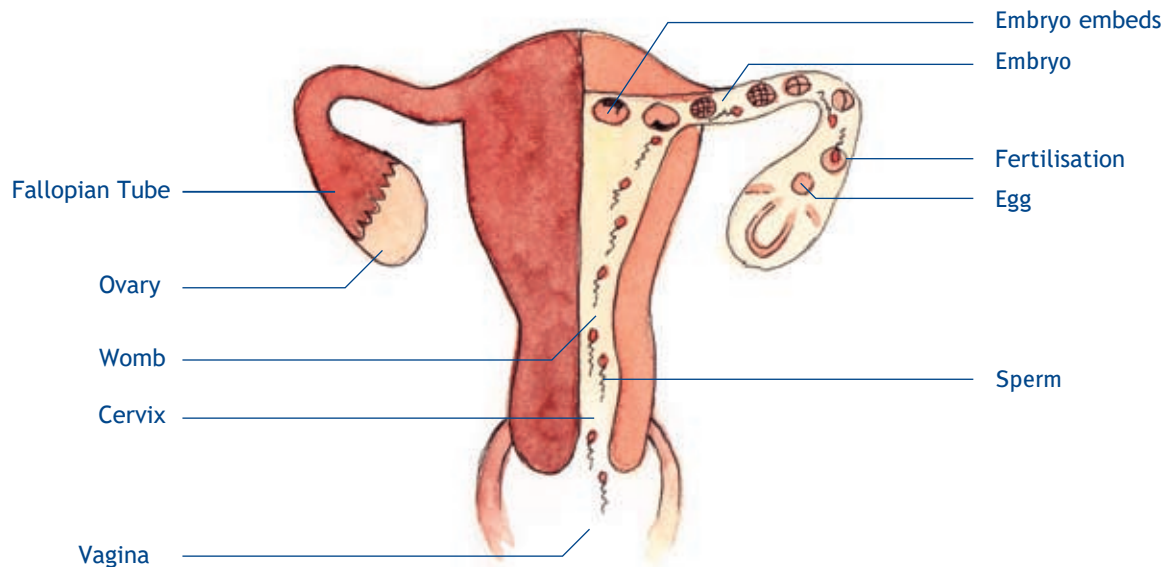


Figure 4 shows the sperms' path to fertilising an egg.

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 reflect the present state of research and are still being tested. We can estimate a girl's fertility and reserve of eggs, by assessing her sexual characteristics and menstrual cycle (periods) and doing some hormone tests. This is particularly advisable if your treatment started after puberty and if you had one of the treatments listed below, as this puts you at high risk of reduced fertility.

- Radiotherapy of the pelvis with a dose of around 10 Gray or more to the ovaries, if the pelvic area is affected by cancer, or sometimes if you have radiotherapy of the spinal cord, as part of brain tumour treatment.
- Whole body radiotherapy (total body irradiation) of around 10 Gray or more, previous to a stem cell transplant.
- Busulfan chemotherapy, from a dose of about 14 mg/kg of body weight, as part of a stem cell transplant.

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



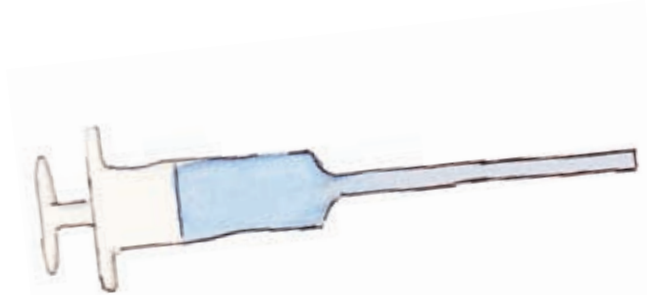
low risk

For more information on the therapy optimization study protocols of the Society for Pediatric Oncology and Hematology (GPOH), please visit: www.kinderkrebsinfo.de.

How can my fertility be assessed?

A basic examination to assess fertility usually involves:

- Taking a medical history.
The doctor will be particularly interested in your periods and any hormones you've taken.
- A physical examination.
The doctor will be looking out for breast development and pubic hair.
- Hormone tests:
These will measure the sex hormones LH, FSH, oestradiol and AMH in your blood between days 3-5 of your menstrual cycle. AMH is a good measure of fertility and shows how many eggs a woman still has. It will be important to know at the time the blood sample is taken whether you have taken any sex hormones, including 'the pill', 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. In some cases a girl's periods stop for a while after chemo or radiotherapy and then start again. They can sometimes disappear for as long as 18 months.



We can measure the stock of eggs left more accurately with an ultrasound scan of your tummy. If tests repeatedly show reduced fertility, it's advisable to start planning a family earlier and possibly taking measures to preserve your fertility.

Will my child be healthy?

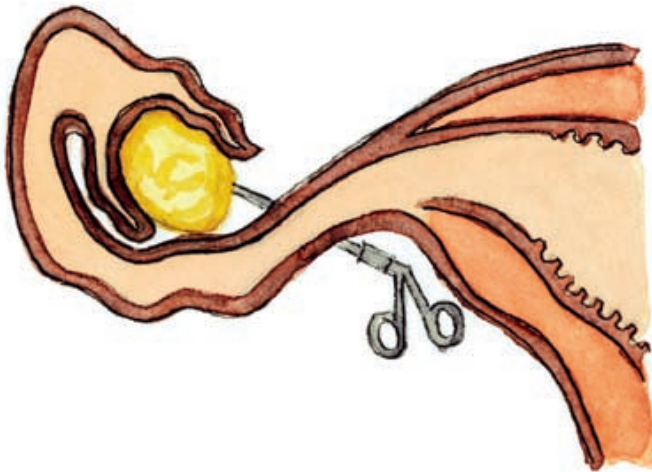
Many cancer patients worry that their children could get cancer too. But lots of research studies, involving thousands of people in Europe and the USA, have shown that the children of people who have had cancer are at no greater risk of either birth defects or of getting cancer themselves. We are currently 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

If you already have maturing follicles in your ovaries we can remove some eggs before your treatment begins, using a procedure known as egg collection or follicular puncture. Before we do this, you would need to take hormones for 14 days. The eggs can then be frozen and stored, if necessary, for many years. Whether the start of your cancer treatment can be delayed by 14 days will depend on the type of cancer you have, and will have to be discussed with the doctors treating you. After you've recovered, your eggs can be thawed and artificially fertilised, if you ever want to have children and haven't been able to get pregnant naturally. There's a 20 - 40% chance of achieving pregnancy like this.



If you are in or past puberty, there is also the option of taking and freezing tissue from your ovaries, containing mature eggs, before your treatment starts. You don't need to take hormones for this to be done. The tissue can then be transplanted back into the ovary after you've recovered. But we would only do this when you actually want to have children, as we don't know how long the re-transplanted tissue will remain functional. Transplanting the tissue back should also result in you producing your own hormones again. But this procedure requires keyhole surgery and isn't yet routine.

Figure 5 taking a sample of ovarian tissue



Before we re-transplant tissue back into your ovary we need to make sure that it doesn't contain any malignant (cancer) cells. This is a particular danger with leukaemias, but also with other cancers that are spread through the blood. In this case, instead of transplanting the tissue back, we would take out individual eggs and use them for artificial fertilisation.

Before and after puberty

If you need to have radiotherapy of your pelvis, you can have an operation to reposition your ovaries away from the path of the rays, before the treatment starts in order to minimize the damage. There are some risks to this operation and later complications can also arise, such as reduced blood supply to the ovaries. In addition, since your ovaries will be removed from the radiation field, cancer cells from other organs that are sometimes found in the ovaries will not be treated by radiation at that time. Before the ovaries are returned to their original position, we will need to consider whether further radiotherapy of the pelvis is likely, and whether the temporary position we've put your ovaries in, will stop them from working well in the longterm. This can be monitored with ultrasound scans.

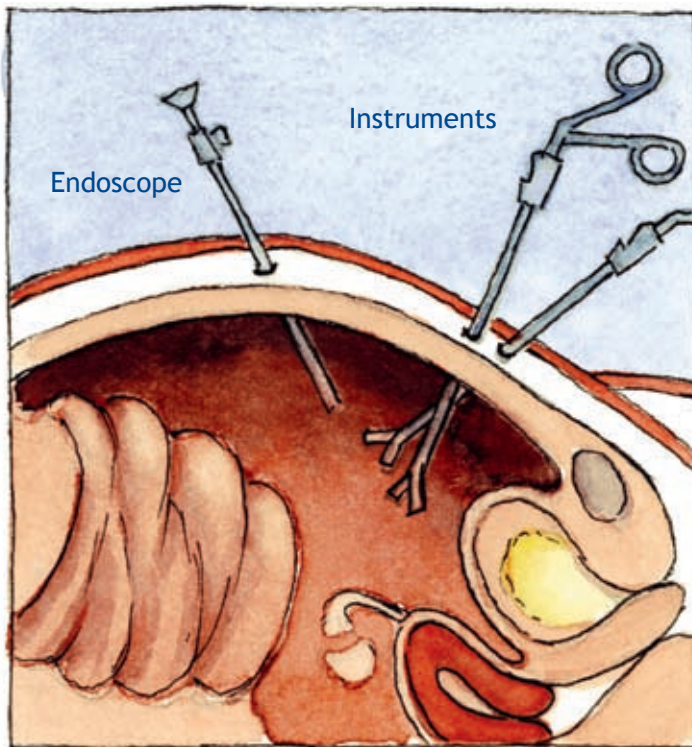


Figure 6 shows keyhole surgery to reposition the ovaries.



Before puberty

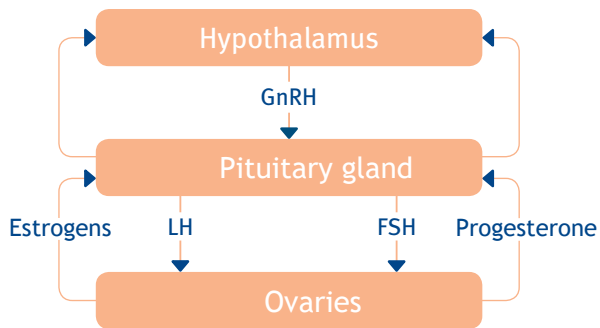
Before puberty, we can take and freeze tissue from your ovary containing immature eggs. The methods for getting the eggs to mature are still experimental, so not yet routine. Even so, some hospitals can offer this treatment to girls who are at particularly high risk of reduced fertility. But at present, only a very few places can subsequently deal with the tissue samples. The preparation of the samples and further processing will only be possible in special centres in Germany.

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



What does hormone replacement therapy involve ?

Your treatment can bring on an early menopause. If you start to get symptoms like hot flushes, sleep problems, feelings of depression or panic attacks, these can be reduced by taking replacement sex hormones (estrogens). You can take these in tablet or patch form, and they will be supplemented by hormones produced by the corpus luteum in your womb.



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

If you've had radiotherapy of your head of more than 30 Gray, your hypothalamus may have been damaged, leading to a shortage of the hormone GnRH and loss of function of the pituitary gland and ovaries. In this case you can have doses of the hormones LH and FSH, either by injection or through a pump, that mirror the rhythm in which they would normally be produced by your pituitary gland.

What about artificial fertilisation?

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 procedures:

- 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).

If you want children, and fertility tests after your treatment repeatedly show a low egg count, you can decide whether to try to have children quite quickly, or whether to improve your chances of having your own child at a later date by freezing eggs or ovarian tissue, if necessary with the help of artificial insemination.

For more information on fertility after cancer treatment, visit www.fertiprotekt.de. Here you can also find addresses of experts for diagnosis and therapy of fertility disorders and experts in reproductive medicine for fertility treatment after chemotherapy and radiotherapy in your area.

Intracytoplasmic sperm injection (ICSI)

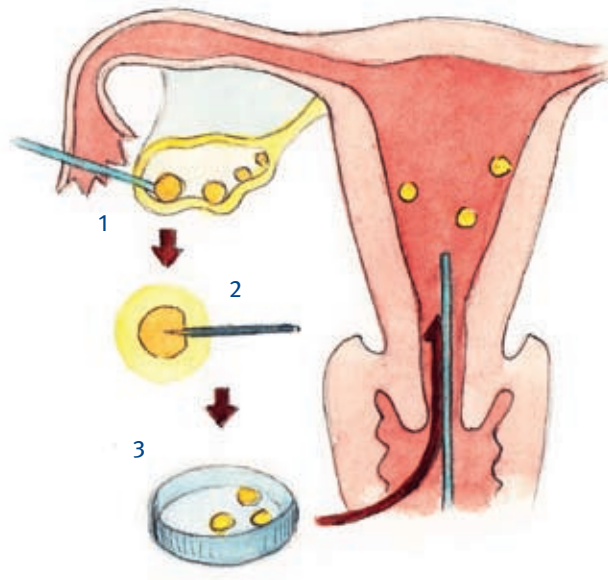


Figure 7 shows a puncture of the ovary (1), artificial fertilisation by inserting a single sperm into an egg (2) and placing the embryo into the lining of the womb (3).

Adopting

If you want to become a mother, 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 mother - 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 centers throughout Germany:

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

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Appendix

The costs of fertility treatment

Something to discuss with your parents

The cost of the hormones for ovarian stimulation is about 1,500 to 2,000 euros. The cost of treatment for ovarian stimulation and egg collection is about 500 euros. Freezing of unfertilised or fertilised eggs costs 150 to 350 euros; freezing of ovarian tissue 350 to 550 euros. Storing unfertilised or fertilised eggs or ovarian tissue about 250 euros per year.

The cost of fertilisation of eggs by in vitro fertilization (IVF) is about 500 euros, by intracytoplasmic sperm injection about 1,500 euros.

German health insurance companies usually pay for the surgical extraction of ovarian tissue. 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.

The freezing of ovarian tissue as a health insurance benefit is currently still under discussion. In individual cases, it is worth asking the local support association for assistance.

The approximate costs for the collection, freezing and storage of the oocytes/eggs/ovarian tissue and for artificial insemination can also be found at: www.fertiprotekt.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 Induktion; 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;
 - 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,
 - 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 ovarian function, 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

"Lucy might want kids one day"
An information brochure with video for adolescent female
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 1st edition:
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



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Picture
Book
of
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Year