

Fertility: it's up to doctors to think ahead

→ Emma Mason

Young cancer patients should feel lucky to survive, and stop fussing about their prospects of having children. This attitude, though still widespread, is now being challenged by many patients and doctors, who argue that it is inexcusable to prescribe treatments that could render a patient infertile, without a thorough discussion of all the options.

A Belgian woman made medical history in September 2004 when she became the first mother to conceive and give birth to a baby after an ovarian transplant following her successful treatment for cancer.

For Ouarda Tourirat, 32, the arrival of her daughter, Tamara, was a dream come true. The achievements of her team of doctors, led by Jacques Donnez at the Catholic University of Louvain in Brussels, gave hope to hundreds of other women who were facing similar prospects of possible infertility after cancer treatment.

Tourirat had been diagnosed with stage IV Hodgkin's lymphoma in 1997 at the age of 25. Before she underwent chemotherapy and radiotherapy, Donnez and his team extracted strips of ovarian tissue from her left ovary and froze them. The cancer treatment cured her Hodgkin's lymphoma, but left her infertile.

In 2003 the frozen ovarian tissue was thawed and reimplanted just below her right ovary. Five months later her menstrual cycle was restored and in January 2004 she became preg-

nant naturally, without assisted reproduction technology.

In his *Lancet* paper (vol 364, pp 1405-1410), Donnez wrote: "Our findings open new perspectives for young cancer patients facing premature ovarian failure. Ovarian tissue cryopreservation should be an option offered to all young women diagnosed with cancer, in conjunction with other existing options for fertility preservation, such as immature oocytes [egg] retrieval, in-vitro maturation of oocytes, oocyte vitrification, or embryo cryopreservation [freezing]."

However, the medical world reacted more cautiously. Two letters in a subsequent issue of *The Lancet* (vol 364, pp 2091-2092 and 2093-2094) pointed out that it was not yet safe for this experimental procedure to become standard practice. Not only did the treatment have a very low chance of success, but also it was arduous and invasive, there was a risk of the original cancer re-seeding itself from the transplanted ovarian tissue, and important ethical and legal issues needed to be addressed.

The case of Tourirat is a good example of



Baby Tamara, pictured here with her parents Ouarda Tourat and Malik Bouanati, was conceived naturally after her mother received pioneering fertility preserving treatment. The procedure, which involves removing ovarian tissue and reimplanting it following cancer treatment, offers hope to many young women, but it is still highly experimental and many safety concerns remain

sider fertility and fertility-saving treatment options as much as possible. It is important both for the doctor to consider it and for the patient to know that you are considering it," she said. "Doctors have to take a proactive role, especially with the young ones who will never talk to you spontaneously about it. Often, boys and young men will say they don't want to think about fertility, they don't want to take more time out of their lives to go to clinics to give semen samples, they just want to be cured, and then you have to push them to think about it."

Discussing fertility serves another purpose too, believes Fosså. "With a young boy it is giving a very important, indirect message that you believe that they will be cured and life will continue. Many patients don't believe that they will survive, but if you do these things to preserve their fertility you are telling them life will go on. It's very important psychologically for young men to freeze semen."

Antonella Surbone, Head of the Teaching Division at the European School of Oncology in Milan, Italy, and a breast cancer specialist, said that fertility issues are a major concern for young patients. In a 1996 study, patients treated for Hodgkin's lymphoma ranked fertility amongst their top three concerns, along with whether or not they were going to be cured and whether or not the cancer might recur. As such, it is one of

some of the technical and ethical problems that confront oncologists and fertility experts when treating patients of reproductive age with a diagnosis of cancer.

Many oncologists and patients would agree on one thing, however: it is vital that cancer patients should be given an opportunity to discuss issues and explore options related to their fertility before any treatment is begun that could render them infertile.

THE DOCTOR'S DUTY

Sophie Fosså, a urologist who specialises in testicular cancer at the Norske Radium Hospital in Oslo, Norway, sees patients of all ages and believes that it is her duty to raise the issue of her patients' future fertility with them.

"It's very important that as a doctor you con-

Vickie Maye

diagnosed age 25



On September 11, 2001, as people worldwide watched in horror as two passenger jets smashed into the World Trade Center in New York, Vickie Maye was staring at an X-ray of her chest.

“Right in the centre, extending across my ribs, there was a grey blur, almost like a cloud. Just a couple of hours earlier, a doctor had told me it was ‘abnormal’. Two weeks, two biopsies and many sleepless nights later, I was told I had cancer. I was 25 years old.”

Vickie is from Ireland but was working as a journalist in Australia at the time, and while her boyfriend, also a journalist, was working flat out on the biggest story in decades, she was having to grapple with a diagnosis of Hodgkin’s lymphoma.

“The diagnosis blew me away. It came as a complete shock.”

The cancer had only been discovered because the Department of Immigration required a medical examination, including a chest X-ray to rule out tuberculosis, before it considered her application for residency in the country.

Vickie was treated with chemotherapy (ABVD) and radiotherapy, but right from the start she wanted to know about the effect the cancer and its treatment would have on her fertility.

“Fertility was a big issue for me. It was one of the first questions I asked, after was I going to die and was I going to lose my hair. The thought of having no kids haunted me. My haematologist told me that the treatment he was giving me, ABVD, was going to give me a better chance of not being permanently infertile. I knew the chances were good but they couldn’t give me guarantees.

“My haematologist was amazing, but his main concern was to get rid of the tumour. While he gave me treat-

ment that had been shown to have less impact on fertility, he simply wasn’t clued in on the ins and outs of it all.

Incorrectly tested

“Soon after treatment, I asked my haematologist if I could have my fertility tested. He agreed and arranged the necessary blood tests. When we got the results, two of the three levels showed I was post-menopausal. I was beside myself. He told me to relax, that he would repeat the tests again in a few months. I simply couldn’t wait another three months. The stress was too much. So I took it upon myself to see a fertility expert. He told me that to test fertility, bloods need to be taken on day one or two of a woman’s period. The samples were taken at the right time and my fertility was found to be normal. The soaring levels previously recorded were simply a result of incorrect timing.

“This was the only issue I had with my treatment: the apparent lack of communication that existed between fertility experts and cancer specialists. While I appreciate that my doctor’s focus was to cure me of cancer, fertility was naturally a concern to me in my 20s and should have been addressed appropriately.”

Soon after her treatment finished, Vickie returned to Ireland where she now works on the *Irish Independent*. Aged 29, she is in remission, her ovarian function has returned to normal and in July she is due to give birth to a daughter, Mia, conceived naturally without assisted reproduction technology.

“I waited two years, as recommended by the doctors, before becoming pregnant. While I had had fertility tests done, I still had this awful feeling that I would be unable to simply fall pregnant. I imagined I would have to face IVF [in-vitro fertilisation]. It used to haunt me. So she is a little miracle!”

Fertility was a big issue ... the thought of having
no kids haunted me

the primary issues that oncologists should discuss with their patients, not necessarily in their very first consultation, but very soon afterwards.

“Oncologists need to know about treatment choices, both in terms of efficacy in dealing with the cancer, and in terms of the degree of toxicity and the effect it might have on the patient’s fertility. You have to make a treatment choice, offer a treatment choice, and evaluate whether you are going to give a treatment that has *x* risk of causing infertility versus one that has half that risk. It’s inexcusable for an oncologist to prescribe without knowing about the spectrum of toxicity, especially fertility, knowing this is one of patients’ top concerns,” she said.

Surbone says that both oncologists and their patients need to know three things. “Fertility can be impaired due to factors unconnected with cancer, such as hormonal disturbances, sperm quality, smoking and alcohol; this is still a hypothesis, but fertility may be impaired by the cancer itself; and, fertility can be impaired by the cancer treatment.

“These need to be explained to the patient, although, as an oncologist, I can only look at the third aspect when discussing treatment options with my patients.”

Unfortunately, not all oncologists are willing or able to discuss fertility with their patients, and nor do they always communicate with or refer patients to fertility clinics, as Jan’s story (below) and the other case studies (pp. 48, 51, 52) show. Jan, from southern Germany, was diagnosed with chronic myeloid leukaemia (CML) three years ago when he was 28. He still feels angry about the way the subject of his future fertility was handled.

“The diagnosing doctor didn’t really tell me about impacts on fertility and about freezing semen before starting a therapy – he would have put me on chemotherapy right away. Luckily, I wanted to know all my options before taking any drugs, so I drove all around Germany to receive second opinions from several doctors. One inter-

nationally renowned specialist in CML research, who is still my trusted doctor today, calmed me down and said that for CML there was no reason to hurry into any treatment. I should make up my mind first about my preferred therapy, bank sperm and then start a treatment in a few weeks.”

TIME TO CONSIDER

This is what Jan did and he is glad that he took the time to find out. “After receiving a diagnosis of CML, nothing was more far away than thoughts of family planning. But look at my situation today: the treatment works successfully, the illness is currently under control and normal life has returned. I am 31, happily married, in a normal job, and hoping for a long life. It would be devastating not to have had the chance to take precautions to preserve my fertility. This is something young patients have to be made aware of before starting any cancer treatment.”

But Jan raises two fears that are worries for patients and their doctors: will the cancer or genetic mutations arising as a result of it or its treatment adversely affect any offspring, and will his own cancer recur while he is trying to start a family with his wife?

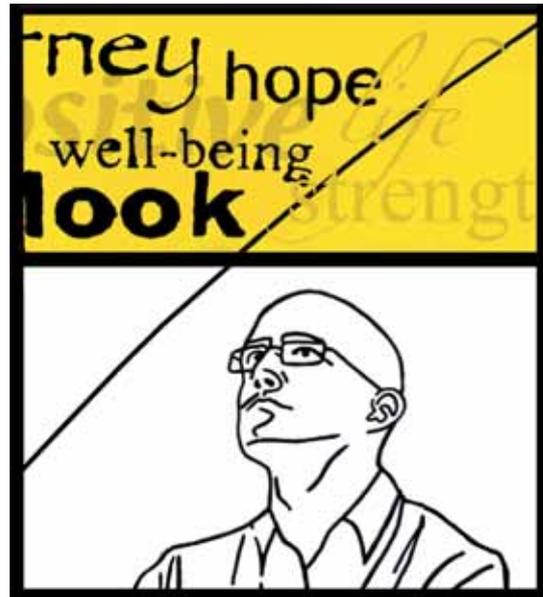
Jan’s CML is held in check with Glivec (imatinib), a newly-developed drug, which is still being tested in clinical trials. “Even though Glivec has been in use for four years, there is little official data on fertility. I am in touch with more than a dozen patients who have fathered children during Glivec therapy, ignoring any warnings, and all babies seem to be very healthy. But who knows in the long term, and who collects the data?

“Additionally, stopping the drug before fathering would be one option, but who knows that conception would be immediate? Stopping therapy would give my illness an opportunity to proliferate; so this is risky as well. We also don’t know whether in-vitro fertilisation will induce

“It’s like trying to back a horse without knowing
how many horses are running or in which race”



Dan Savage (see also box opposite) created 13 paintings focusing on his experience of cancer, including its potential impact on his fertility. The images were displayed last May at the conference of the Teenage Cancer Trust, for which he acts as an ambassador in the UK



additional risks and strains – for my wife as well as for the baby. We already made one attempt that failed, so we know this way is not the easiest.

“Therefore, we’ll have to decide between the risk of conceiving whilst on the drug, the risk of stopping the drug, or the risk of in-vitro fertilisation. All their life, young cancer patients like myself have to decide on uncertainty.”

Jan has put his finger on the crux of the problem that confronts cancer patients: it is rare for there to be a treatment option that is clearly the best path to take. Patients and their doctors constantly have to weigh up uncertainties, trying to choose the treatment that is most efficacious while also fitting in with the patients’ aspirations for the future.

NO SURE BETS

Sarah Gahan, 42, a breast cancer patient who is now in remission (see p. 52), said: “There are lots of choices, but no obvious right way or tidy decision that can be made, and sometimes the doctors and scientists are as much in the dark as you are.

“My tumour was oestrogen positive, and with this type of tumour the question is whether trying to become pregnant and pregnancy itself might make the tumour grow more. And the answer is that nobody knows. It’s like trying to

back a horse in a race when you don’t know how many horses are running or in which race.” This is where good communications and relations between doctors and their patients are vital, so that patients feel that they are able to make fully informed choices about their treatments, with support and advice from a doctor they trust.

Both Fosså and Surbone point out that oncologists need to consider fertility issues when their patients have any cancer where the treatment involves chemotherapy or radiotherapy, both of which can damage fertility either temporarily or permanently, and not only when the cancer is related to the reproductive organs (as with testicular, ovarian, endometrial or breast cancer).

In many ways, the options open to boys and men when confronted with a diagnosis of cancer are easier than for girls and women. Men can have their sperm frozen and the sperm do not suffer too much during the freeze-thaw process. The sperm can then be used at a later date to fertilise a partner’s eggs by in-vitro fertilisation, sometimes using intra-cytoplasmic sperm injection (ICSI) to make sure the sperm reaches the egg successfully.

Even for younger boys who are not yet able to ejaculate sperm, there is a possible solution. Fosså said: “Sperm can be extracted under

Dan Savage

diagnosed age 20



Dan, 22, was studying art at Lancaster University when he discovered a lump the size of half a pea in his right testicle two years ago.

“I was actually checking my testicles because a teacher of mine at school had had testicular cancer and he told us all to check our testicles regularly, so I did. The doctor thought it was a cyst, but I pressed a bit harder and he referred me to the hospital. Ultrasound showed it was stage I testicular cancer. I was lucky because I caught it early. I had the operation at Lancaster and then was transferred to St James’s in Leeds for chemotherapy.

“The chemo was largely precautionary. The outward appearance of the tumour suggested it was early, but when they dissected it, they found it was quite developed, just on the brink of spreading and they didn’t want to take that risk.

“The doctors talked about fertility before they gave me chemo. It came as quite a shock, and I hadn’t considered it. It was very sudden from that point on, as I

had to go to the fertility clinic twice to provide sperm samples, once three days before I started chemo and once on the very day I started my chemo.

“I think that you should know about fertility issues beforehand, especially as at my sort of age and a bit older you start to think about starting a family, and it’s important. I think I’d probably wait a few more years before starting a family, but I would like to have children while I’m still in my 20s.”

Dan is now in remission, but goes for regular checks. He was keen to highlight one particular aspect of his experience. “Two months before my cancer was diagnosed I had a swelling of my breast tissue. When you are about 14 or 15 you have that feeling and it is to do with the maturing process, so I thought it was the hormones, but actually it was the testicular cancer. No one has ever mentioned this as a symptom, and it’s quite important that people know about it. Had I known, I might not have needed chemo, as the testicular cancer would have been caught months earlier.”

It came as quite a shock when the doctors mentioned fertility

anaesthetic, although the success of this is not clear yet, and it’s very important for these young boys that you don’t over-treat.”

TECHNICAL CHALLENGES

For girls and women, the options are more complicated. The female ovary contains its full complement of eggs at birth. However, techniques for freezing eggs have not been very successful so far, with the egg suffering severe damage during the freeze-thawing process. Therefore, a woman has to have a partner who can provide sperm so that any eggs retrieved can be fertilised immediately, allowed to start developing into an embryo in vitro and then frozen until it can be implanted in the woman when the cancer treatment has finished and she is ready to start a family. For girls or women

without partners, this is not an option open to them, nor is it available in many countries.

However, it is possible to freeze and thaw successfully whole ovaries or strips of ovarian tissue. Eggs can be retrieved from the thawed tissue, matured in vitro, then fertilised and any resulting embryos implanted. Or, as the case of Tourirat shows, the ovarian tissue can be transplanted back into the woman, although this is at too experimental a stage to be considered a standard option.

Where radiotherapy is part of the treatment, it is sometimes possible to remove the ovaries from the radiation field. Some drugs used in chemotherapy have a less severe effect on fertility, both for men and for women, than others, and it is quite possible for fertility to be restored once the treatment has finished. A common theme amongst the cancer patients featured here

Sarah Gahan

diagnosed age 36



Sarah Gahan, 42, and her husband had been trying to start a family for 18 months without success when she discovered she had breast cancer at the age of 36.

“I found a lump in my right breast, which didn’t worry me at all because I’m used to having bumps on me from lipomas [small benign, slow-growing tumours that come from fat cells and which are not cancer]. I had it checked out and it was a bit of a bomb shell to find it was cancer.”

Just over two weeks after her cancer diagnosis, Sarah had a lumpectomy and her lymph nodes removed (to see whether the cancer had started to spread), followed by chemotherapy. Initially, her doctors did not mention fertility to her, and it was only after she researched breast cancer on the Internet and brought the subject up herself that it was discussed.

“The unspoken attitude is still very much ‘Why are you worrying about your fertility when we are trying to save your life?’. It was just not considered an issue. I found it a bit patronising,” said Sarah, who lives in London.

“I hit lucky with the consultant oncologist that I saw. He is heavily into research and he understood about young women and fertility. He tried to get me onto a trial to have epirubicin, but he also made a call to an ART

[assisted reproduction technology] facility, where a woman saw me the same day in her lunch hour.”

Frozen embryos

As a result, Sarah was able to have eggs retrieved from her ovaries in her next cycle and she started chemotherapy immediately afterwards. The eggs were fertilised with her husband’s sperm via ICSI (intra-cytoplasmic sperm injection), creating seven embryos, which were frozen. In remission and approaching 40, Sarah and her husband John decided to try to start a family. The best three of the frozen embryos were implanted together, but unfortunately Sarah failed to become pregnant. At present she is not planning to use the remaining embryos, but psychologically it helps her to know that they are there if she changes her mind.

“I think I may be ovulating naturally now, and if I become pregnant naturally that would be wonderful.”

She pointed out that young women of her age represent a very small proportion of breast cancer patients, but for them, fertility is likely to be a big issue. “I needed more information, up front, and breathing space. Unless a woman’s cancer is going to kill her in the next two weeks, then give them time to think about it. There are lots of difficult issues to come to terms with.”

The unspoken attitude is still ‘Why worry about fertility when we are trying to save your life?’

is that not only would they have liked to have the options for fertility discussed openly with them up front, but also that they needed more time to assimilate the information and make decisions.

Gahan said: “The decision-making process at the beginning was too hurried, and it was the medical profession that was pushing it forward. I needed more time to come to terms with the diagnosis, more time to consider choices and more time to consider fertility issues.”

Estimates suggest that one in a thousand peo-

ple is a cancer survivor, due to increased prevalence of the disease and improved treatments. Surbone and Fosså believe this makes it imperative for physicians to take the time to discuss all available options with their patients and to consider fertility preservation as an integral part of patient care.

Vickie Maye, 29, who is in remission from Hodgkin’s lymphoma and pregnant with her first child (see p. 48), sums it up: “Cancer is not a death sentence. You can live a full life, so why should you not be able to have a family?”