

# Cancer in pregnancy: the cruellest dilemma

→ Anna Wagstaff

When a pregnant woman discovers she has cancer, her doctor faces a challenge with few guidelines, and little evidence of optimal treatment. The woman faces a cruel dilemma – does she lose the baby to save her life, or risk her life to try to save the baby?

**P**regnant women are rarely diagnosed with cancer. The incidence is around one case in every 1000 pregnancies, but it has been rising for some time, largely due to the trend towards delaying starting a family. It poses a unique set of problems, which vary according to the stage of pregnancy, and the nature, location and stage of the cancer.

Treatment that may be essential for the mother may be fatal or highly damaging to the fetus. Achieving the best outcome possible in the circumstances is a real challenge for the physician.

## 40 WEEKS: THE BABY'S STORY

A normal full-term pregnancy lasts around 40 weeks. It is perfectly normal for babies to be born up to two weeks early. Delivery at 36 weeks is unusual, but, while not ideal, is

considered fairly safe nowadays. In cases of real need, babies can be induced at 30 weeks in specialist units under the care of expert obstetricians, who use steroids to speed up lung development.

This is not an ideal start in life, and spending weeks in an incubator is also not the best start to any mother-child relationship. Moving the delivery date any earlier is dangerous and runs a high risk of long-term health consequences.

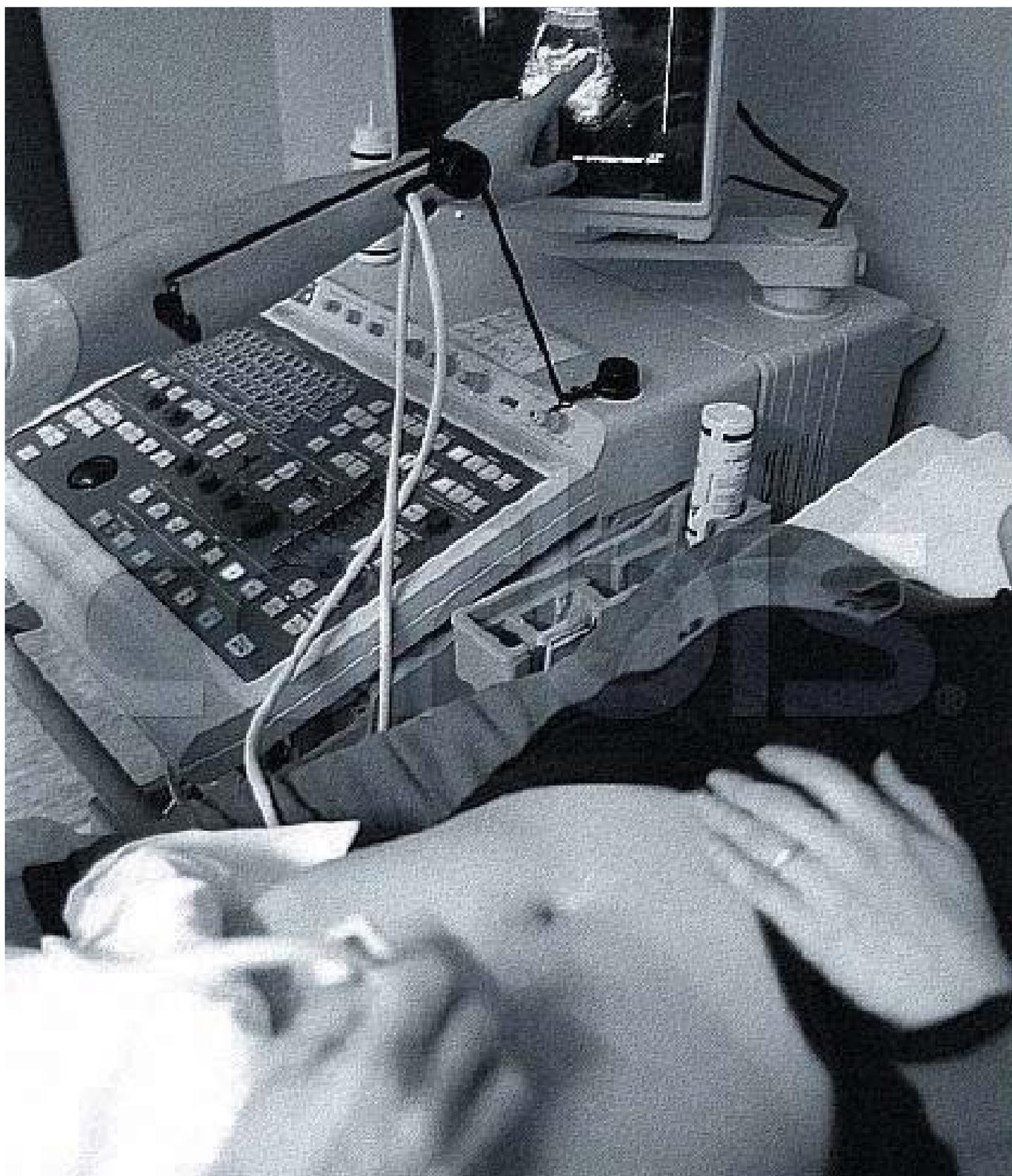
## 40 WEEKS: THE MOTHER'S STORY

For a woman diagnosed with cancer, waiting 40 weeks for treatment could be a death sentence, particularly with high-grade, aggressive or metastatic cancers. Even in earlier or more indolent cancers, a 40-week delay would be reckless, allowing the cancer the opportunity to develop and spread into incurable disease.

## THE MEDICAL DILEMMA

In this situation, there are not many options, and none of them are ideal. One option is to delay the treatment until the child can safely be delivered. This poses a risk to the mother that may be hard to quantify. It also means she will have to care for a very premature baby while coping with the side-effects of cancer treatment. This option is more viable the lower the risk posed by the cancer and the more advanced the pregnancy.

A second option is to terminate the pregnancy to allow normal treatment to go ahead. This may be the safest option for the mother's health, but will be unacceptable to some mothers who do not accept abortion on any grounds. Leaving the mother without her baby is a particularly heavy blow given that the treatment may make it impossible for her to have any more children. This option is more likely to



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## LATE DIAGNOSES

Cancer in pregnancy is often detected later because symptoms are masked by other body changes.

- Engorged breasts make it harder to detect breast cancer, and palpable lumps are often misdiagnosed as blocked milk ducts.
  - Signs of cervical cancer may be misunderstood. One woman was hospitalised twice because of vaginal bleeding, wrongly attributed to complications with the pregnancy. Cervical cancer was diagnosed only after the baby was delivered by caesarean section, by which time it had spread.
- Midwives and obstetricians must be aware of the need to rule out cancer when presented with these symptoms.

be considered early in pregnancy, when an abortion may be less traumatic and when the patient would otherwise have to wait a particularly long time for treatment.

A third option is to treat the cancer as effectively as possible while continuing the pregnancy and trying to minimise the risk to the fetus. The trouble is, there is still a lot we do not know about those risks.

The decision is not helped by difficulties in ascertaining how far the cancer has developed. Some staging techniques, such as certain blood tests, cervical cytology and mammography, are unreliable in pregnant women because of changes associated with pregnancy. Others, such as cone biopsy of the cervix early in pregnancy, CT scans, abdominal X-rays and any form of radionuclide imaging, are dangerous to the developing fetus. While ultrasound and MRI can be used as suitable alternatives, checking whether the cancer has spread to other organs or bones can be very difficult, and doctors may have to develop a treatment plan on the basis of an incomplete picture.

### WHERE'S THE EVIDENCE?

The treatment of cancer in pregnant women is a grey area within a disci-

pline that is increasingly dominated by evidence-based medicine built on data from ever greater numbers of clinical trials. The extra risk posed by delaying treatment a couple of months or the dangers to the fetus of, for instance, administering hydroxyurea in the first trimester are not the stuff of randomised controlled studies. New drugs are coming onto the market all the time, but there is no information about how they are likely to affect embryonic or fetal development. For this sort of information we have to rely on case reports, and it is only recently that attempts have been made to gather the information together by collecting published case

reports and series or by setting up prospective registers.

Take radiotherapy. The dangers of radiotherapy to the developing embryo/fetus are relatively well known (see box) from studies after the bombing of Hiroshima and the Chernobyl disaster. While no one would contemplate delivering radiotherapy to the cervix or abdominal area during pregnancy, there is no consensus on the dangers posed by radiotherapy above the diaphragm.

Antonella Surbone, who worked as a specialist in breast cancer and pregnancy at the Memorial Sloan-Kettering Cancer Center in New York, believes that radiotherapy should not be used at all in breast cancer during pregnancy. Sibylle Loibl, from Frankfurt University Women's Hospital and the German Breast Group, is heading a study into treatment of breast cancer in pregnant women under the umbrella of the Breast International Group (BIG), with a view to drawing up international guidelines. She is also strongly opposed to the use of radiotherapy during pregnancy, but says that other experts involved in drawing up the guidelines are more open to the possibility.

## RISKS OF RADIOTHERAPY

Radiotherapy is contraindicated in pregnancy, although some specialists use it above the diaphragm with abdominal shielding, particularly in later stages of pregnancy.

Therapeutic doses of 5000–6000 cGy expose the fetus to 10 cGy in early pregnancy and 200 cGy or more in later pregnancy

Doses over 2.5–5 cGy pose a high risk for malformation in early pregnancy.

### Likely effects

From conception to days 9/10

Weeks 2–6

Weeks 12–16

Weeks 20/25 to birth

lethal

malformation, growth retardation

mental and growth retardation, microcephaly

sterility, malignancies, genetic defects

# Treatment that may be essential for the mother may be fatal or highly damaging to the fetus

Jacek Jassem, a leading Polish oncologist who specialises in both radiotherapy and medical oncology, believes the risk is relatively small. He argues that “If you are pregnant and the cancer is located in the supraclavicular left node, you can safely radiate the patient above the diaphragm with shielding of the abdomen, even in the first trimester.” He says that there is a small risk to the fetus, and he would not recommend radiotherapy lightly. However, he would consider it as an option, for instance, in cases of Non-Hodgkin’s lymphoma requiring immediate treatment, if the mother did not want to abort. These differences are reflected in

analyses of case reports of breast cancer in pregnancy gathered from the literature. In some studies the majority of women were treated with radiotherapy, while in others radiotherapy was never used.

When it comes to chemotherapy, the picture is not much clearer. Given that cytotoxic drugs are designed to inhibit cell division, they could be expected to damage a developing embryo or fetus. Evidence from laboratory studies, animal tests and case reports show high levels of teratogenicity and fetal deaths for many common drugs delivered in the first trimester. The risk levels in the second and third trimesters are not well established for the majority of

drugs. In the last few years some major studies have indicated that the risk is fairly low for many of the most commonly used, including the AVBD regimen (dacarbazine, bleomycine, vincristine and doxorubicin) for Hodgkin’s lymphoma, a variety of standard treatments for leukaemia and Non-Hodgkin’s lymphomas, and adjuvant therapy for breast cancer.

In the absence of robust evidence, many doctors are reluctant to offer opinions on the safety of these treatments. This may be good science, but some patients object that it leaves them no basis on which to take important personal decisions.

Jan G is a young (male) patient activist from Germany who has chronic myelogenous leukaemia (CML), the same cancer that affected Megan Smith (see Megan’s story, p. 21). He runs the website [leukaemie-online.de](http://leukaemie-online.de), about the condition, and understands patients’ frustration at the lack of information. “All information is so sensitive regarding pregnancy, fertility and so on that nobody is prepared to talk about it nor publish data unless they are 100% certain.

“However, young patients are faced with those issues and have to decide on uncertainty.” He has often thought about building a database where patients can publish their personal ‘Glivec baby’ data, for other young patients to see. “Even if the data are neither comparable nor statistically significant, it would be better than having no indicative data at all!”

## RISKS OF CHEMOTHERAPY

Almost all drugs cross the placental barrier to some extent. As chemotherapeutic drugs work by inhibiting cell division, they pose a risk to the developing fetus.

Chemotherapy drugs are associated with spontaneous abortion, malformations, teratogenesis, mutations, carcinogenesis, organ toxicity and retarded development.

### 1st trimester

Damage is more likely to occur in the 1st trimester. The rate of chemotherapy-associated fetal malformation at this stage of development has been estimated at 12.7–17% with single-drug regimens and up to 25% with combination regimens, compared to a population rate of 1–3%. Low birth weight occurs in around 40% of cases.

### 2nd and 3rd trimesters

Many drugs pose a relatively low risk to the fetus in the 2nd and 3rd trimester. Some doctors prefer to wait until the development of the central nervous system is complete, around the 16th week.

### Delivery

If a baby is delivered within 2 weeks of the last chemotherapy dose there is a risk of a neutropenic baby being born to a neutropenic mother.

### Breastfeeding

Breastfeeding is inadvisable for women who have recently been on chemotherapy.

## Christina Brenne Trusting her instincts



Christina Brenne was pregnant with her second child when she noticed a lump in her breast and mentioned it at a routine check up. Her midwife arranged an appointment with a doctor who told her it was a blocked milk duct. Christina was not convinced, since this was different from her previous pregnancy. The doctor reluctantly referred her to the breast clinic, but with a low priority at the back of the queue.

After six weeks she phoned to ask about the delay in her appointment. There had been a cancellation and she was called in the following day. They did a palpation, a mammogram, an ultrasound examination and a puncture biopsy.

The mammogram showed negative. The other two examinations were both positive.

She was seven months pregnant when she was told by the breast specialist that she did have cancer. The doctor said he had consulted an obstetrician and had made up his mind what to do: her baby would have to be delivered at 32 weeks so they could operate on the breast.

### Sleepless night

Shocked and distressed, she spent a sleepless night before ringing the clinic to press for an alternative plan, but was told that very premature delivery was the only option. It was only at a chance visit to her General Practitioner over an unrelated problem that she learned that operating on pregnant woman was routine.

She called the clinic, demanded the name of the obstetrician who had supposedly refused the operation, and phoned him. He told her he had never raised objec-

tions, and had in fact offered to co-ordinate her care, since the operation would be done by the breast specialist surgeon at his hospital, which had a special obstetrics unit. He now repeated that offer, which she accepted.

She was given a choice between breast conserving surgery and radical mastectomy. She chose mastectomy, because she was very keen for her child to be breastfed, and the surgeon had promised that this option would avoid the need for chemotherapy.

### Let down

The surgery went well and she was happy to be looked after on a postnatal ward, even though the staff were not experienced in surgical cases. However, it turned out that she had the most severe form of cancer. Despite earlier promises, she was now told that she would need to start adjuvant chemotherapy as soon as the baby was born.

Christina felt very let down. She decided to ask for the baby to be induced two weeks early, so she could use that window to breastfeed. Having originally had to fight not to have her baby delivered eight weeks early, she now found that the hospital was slightly reluctant to induce the child even two weeks early. Christina wasn't going to give up now. She won this battle, and breastfed baby Sissela for 17 days.

She gave Sissela a final feed on the hospital bed as needles were being inserted for her first treatment. Christina is now disease free. Sissela is nearing her third birthday, and her older sister Lovisa is seven. Christina's advice to other women is: "Think for yourself – is this really what you want? Always get a second, third or even a fourth opinion."

The doctor said he had consulted an obstetrician  
and had already made up his mind what to do



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## Treating cancer in pregnant women is a grey area in a discipline led by evidence-based medicine

### WHERE IS THE EXPERTISE?

The paucity of evidence on therapy options is not the only problem for doctors. There is also a very small base of expertise – few oncologists come across more than 20 or 30 of these rare cases in their entire career, most will come across far fewer. Surbone says it is important that clinicians recognise their own limitations, “If you get such a patient, try not to handle the case on your own. Refer the patient to a centre where they have experience, where they have a joint oncology/ObGyn service.” If this is not possible, a close working relationship between the oncology team and the obstetrics team is vital. The story of Megan Smith, the CML patient treated in Toronto by a leukaemia specialist working with the head of a high-risk obstetrics unit, is

an example of what can be achieved (see p. 21). The story of Christina Brenne in Sweden (see p. 18), shows what can happen when breast cancer specialists don't work well with obstetricians – in this case, despite the obstetrician's advice, her specialist insisted she had no option but a very premature delivery, because he would not recommend surgery while she was seven months pregnant.

Loibl says that many German doctors insist on a very premature delivery in preference to giving the patient adjuvant chemotherapy, even in late stages of pregnancy. She attributes this to the fact that breast cancer in Germany is treated by gynaecologists, many of whom do not specialise in oncology and lack expertise in chemotherapy. As well as underlining the need for breast cancer to be treat-

ed by specialists, this illustrates the need for expertise in both obstetrics and oncology in treating a pregnant woman with cancer.

### WHERE ARE THE GUIDELINES?

Many physicians would welcome guidelines to point them in the right direction. These are hard to come by, even in breast cancer, the cancer most frequently diagnosed in pregnancy. The Italian Association of Medical Oncologists is unusual; it does offer guidance on diagnosis, the use of radiation and chemotherapy, recommended surgical procedures and the importance of working with a multidisciplinary team. However, no such guidelines exist in the UK or the Netherlands – two countries that lead the field in clinical guidelines. Nor have guidelines yet been drawn up by

# There is no consensus on the dangers posed by radiotherapy above the diaphragm

the European Society of Mastology. Two separate developments may soon change this. Two years ago, Nicholas Pavlidis of the Ioannina University Hospital in Greece, wrote a paper with recommendations for the diagnosis, staging and treatment of cancers most commonly found in pregnancy and outlining the circumstances under which a termination of pregnancy should be recommended. He has now proposed that the Guidelines Task Force of the European Society of Medical Oncology (ESMO), on which he sits, draw up more formal guidelines, despite the lack of randomised studies or meta-analyses. He says that level 3 or 4 guidelines, which have lower standards of evidence, would be a great deal better than nothing. The second new guideline initiative is spearheaded by Loibl at the University of Frankfurt. In October 2003, she called an international meeting, involving surgeons, oncologists, radiologists and breast diagnostic specialists from MD Anderson in the US, Guy's & St Thomas's in the UK, the Centro di Riferimento Oncologico in Italy and a number of German centres, to discuss and draw up international guidelines on the diagnosis and treatment of breast

cancer in pregnant women. Loibl expects these to be finalised and published early this year.

The Frankfurt initiative is also running what is probably the first prospective study using a standard protocol for treating cancer in pregnancy. It involves the use of breast conserving therapy for women diagnosed with early stage breast cancer after the first trimester. The standard treatment in most countries is a radical mastectomy, on the grounds that breast conserving surgery has to be followed by radiotherapy, which is not advisable in pregnancy. Loibl's team argues that, given the trend to administer chemotherapy for between 18 and 24 weeks, there is no harm done in delaying radiotherapy until the child can be delivered at 36 weeks, and they expect the results of the trial to prove this. If correct, this would establish one of the first pieces of firm evidence in this area of medicine.

Publication over the past year or two of studies bringing together the results of substantial numbers of cases treated with a variety of drugs is another brick in the evidence base. Fedro Peccatori and a team at the European Institute of Oncology are now setting up a European registry for

all patients given chemotherapy during pregnancy, in order to facilitate this process.

## THE MOTHER'S DILEMMA

Lack of evidence, expertise and guidelines represent the challenge to professionals. Whatever the state of the evidence, there is also a painful human dilemma for the pregnant woman, or couple. The three-way choice between terminating a pregnancy, accepting treatment that may cause severe damage to the fetus, or delaying treatment with possibly life-threatening results is one that has to be made by the patient, not by doctors.

Each story is different, as shown by the following examples, which came from doctors and patients in Germany, Sweden, the Netherlands, Poland, Greece, Ireland and the UK, in the course of researching this article.

A woman diagnosed with early stage breast cancer opted for abortion and immediate treatment, because she had two young children dependent on her and was not prepared to take any chances.

A woman with three young children was discovered to have a 5-cm lump, eight weeks into her pregnancy. She underwent a radical mastectomy and

# Patients object that it leaves them with no basis to take decisions of enormous personal importance

## Megan Smith

### Sticking to her convictions

Megan Smith was a 22-year-old biology student from Peterborough in Canada when she went to her doctor with suspected appendicitis. He told her she was pregnant. A minute later he told her that she had some form of leukaemia and she would have to terminate the pregnancy because she needed treatment right away. He said that the drugs would terminate the pregnancy anyway. "It just isn't worthwhile for you going through that stress later on."

Megan and her husband spent two distraught hours in the hospital corridor. "We didn't know what type of leukaemia it was; if I was going to be dead within a few months." They had always wanted children, and were opposed to abortion. When they told the doctor they would not terminate the pregnancy, he said he could not treat her, and referred her to a specialist oncologist in Toronto, two hours drive away.

In Toronto things started to improve. The specialist explained the disease, and spelt out the options. The only cure, he said, was bone marrow transplant, and chemotherapy, which would probably end her chances of conceiving again. He too said she needed immediate treatment and that the drugs would be highly likely to bring about a miscarriage. He strongly advised her to think about an abortion.

Megan and her husband took five minutes to decide they wanted to continue the pregnancy. They were worried that the specialist might refuse to treat Megan, as the first doctor had done. But, once they had made their decision, the doctor backed them "one hundred percent".

The specialist said that delaying treatment risked allowing the disease to accelerate out of control and would make her vulnerable to clotting. He stressed it was their choice, but he did not recommend it. He explained the risk the drugs would pose to the fetus, showing them the results of animal studies, including pictures of the deformities induced. They decided to go ahead with treatment.

Megan was given an initial high dose of hydroxy-

urea to bring her blood count down, followed by the lowest dose possible, to give the fetus the best chance.

#### Searching for information

Together with her husband, she searched the Internet to try to quantify the risk they were running. They found little about results in humans, but noted that the doses used in the animal studies were 50 times higher than she was receiving, which was reassuring.

The oncologist signed her up with the head of the high-risk obstetrics unit in Toronto, at the Mount Sinai Hospital, which runs a programme for mothers with diseases during pregnancy. The hospitals face one another across the road, and the two doctors worked closely together and tried to coordinate appointments so that Megan would not have to make too many trips to Toronto. At around 8 weeks, the specialist got the go-ahead to start Megan on Glivec (imatinib) – permission was needed on account of the cost. She was monitored constantly by both doctors, but she had to wait until the 12th week of pregnancy before it was possible to tell, using ultrasound, whether her fetus had suffered severe damage. She and her husband had decided they would agree to an abortion only if the damage was very severe, such as anencephaly. Waiting for the results was "terrorising". But the news was good, they could see signs of four limbs and a good head shape. Blood tests showed no serious genetic defects. Megan and her husband began to relax a bit.

On October 3rd, 2004, a healthy boy, Connor Charles Moore, was born, weighing 6 lbs 1 oz (2.75 kg). Following the birth Megan's blood count started to rise again; her Glivec dose was increased, and she is now stable. Megan recognises that their decision to go ahead was controversial. She knows of only five instances of babies born to women who were on Glivec, but believes they are all healthy children. Now she wants a second child.



Waiting for the results was terrorising, but the news was good

# Physicians would welcome guidelines to refer to – but they are hard to come by

was found to have 20 positive nodes. She was given eight cycles of chemotherapy, but not until she reached her 3rd trimester.

A woman, pregnant with her first child, was diagnosed with high-risk breast cancer. She agreed to an abortion to allow immediate intensive treatment. The cancer was not cured and she deeply regrets losing a child that could have survived her.

A patient was diagnosed with stage 1B cervical cancer at around 18 weeks. She waited more than three months for treatment and had the child delivered at 32 weeks.

A woman was diagnosed with ovarian cancer while pregnant. She refused her gynaecologist's advice for an immediate hysterectomy and even refused chemotherapy. She had been trying to have a baby for 12 years before she became pregnant. She said: "I don't care if I die, I'm going to leave my baby to be raised by my husband or my mother." Not everyone will share those priorities ... and not everyone has a husband or mother they can trust their newborn to.

These stories illustrate that there can be no right or wrong answer. Women are in different circumstances, with different priorities and facing different possible outcomes. Some women say that the child helps them cope with the cancer. Others feel that a new baby is challenging enough for a healthy woman, and that it may be too much for a woman debilitated by cancer therapy and with other young children at home, to care for a very

premature newborn who may be affected by the treatment.

The biggest question is whether or not to continue with the pregnancy. But there are other difficult questions too, such as whether to induce pre-term delivery, or to risk cytotoxic treatment. If either choice is made, how early should action be taken?

## REACHING A VERDICT

David Luesley, gynaecological oncologist at Birmingham Women's Hospital in the UK, starts consultations by outlining the extreme possibilities. "The best outcome is a healthy mother and a healthy baby; the worst outcome is two lives lost." If aiming for the first means delaying vital treatment, there is a risk the mother will die before the fetus is mature enough to survive, resulting in the worst possible outcome.

Pavlidis uses what he calls the Golden Rules, when teaching students about the treatment of cancer in pregnancy.

1. You have to benefit the mother's life
2. You have to treat curable malignant disease
3. You must protect the fetus from harmful effects
4. You must try to keep the woman's reproductive system intact

These imperatives represent, he says, an order of priority "drawn from the daily practice of a doctor's life." He emphasises, however, that it is ultimately the patient's priorities that take precedence.

In this situation there are rarely good options, just a choice between bad

ones. Some doctors have ethical objections to abortion. Some may have an ethical objection to administering drugs to a pregnant woman, when there is a potentially high risk of severe damage to a fetus. Many are not happy about delaying urgent treatment for a patient at high risk.

A doctor who wishes to do best by his or her patient has to put personal preferences and convictions to one side and focus instead on helping the woman reach a decision that best reflects her own priorities.

Helping women to make that choice demands absolute honesty. Luesley says that breaking bad news to a pregnant woman is one of the hardest things a doctor has to do, and he warns against glossing over stark realities. He cites the example of a pregnant woman with ovarian cancer choosing between radical hysterectomy and chemotherapy. "You have to be clear about the likelihood of response – between 60% and 80% show a response, but a proportion relapse, and can do so quickly."

Surbone points out that you are asking a woman, at a time when she is very scared and vulnerable, to make a decision about the life of her child versus her own life versus her responsibility to this child. "She has to think about surgery and/or chemotherapy. She has to think about the practical implications, and about her relationship with her husband after a possible mastectomy. Added to all this, she now has to think about a child who could possibly grow up without her."



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## It is cruel to have to decide between the risks posed to yourself and to the child you are expecting

The question is, says Surbone, whether you feel your role as a doctor is purely to provide the best information, and that offering any advice is an abuse of power, or whether, while respecting the patient's autonomy, you feel your responsibility as the expert is to offer advice in their best interest.

She herself tends to the latter view. "I first inform my patients fully. But if they ask me: What do you think I should do? I give my opinion, which depends on the case. But I always say 'This is my opinion as a physician. I'm not you, and however I try to put

myself in your position I may never understand your values, and I may not share them.'"

She points out that, as the doctor, you are the expert who has the information and holds the key to the various treatment options, and you are the one who is under the least pressure. In practice, the way you present the information will influence what the patient decides.

Few situations test a doctor's ability to serve the sick as much as this one. It requires good science – evidence-based knowledge about the risks asso-

ciated with the various options and a top-quality multidisciplinary team to oversee the care of mother and pregnancy. It also requires the art of the physician in communicating with the woman and judging what level of advice to offer to get the best outcome for her. Finally it requires a large measure of common humanity. It is cruel to have to decide between risks posed to yourself and to the child you are expecting, and it is unthinkable that such a decision should reflect the priorities and preferences of anyone but the woman herself.

Background reading to this article can be found in:

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And at [www.germanbreast.de/pregnancy](http://www.germanbreast.de/pregnancy) and [www.motherisk.org](http://www.motherisk.org)