Frédéric Amant

building the evidence base for saving mother and child

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Understanding the impact of treating the mother on the long-term health of her unborn child has long been held back by logistical and ethical obstacles to researching this rare patient population. Frédéric Amant took up the challenge.

One of the most astounding pictures to go 'viral' on the Internet recently is of a women breastfeeding her newborn son with her remaining breast after having undergone a mastectomy for breast cancer diagnosed during her pregnancy. Not long ago, the recommended course of action for many invasive cancers detected during pregnancy was an abortion, to then embark on life-saving treatment for the woman.

That's all changed now, in large part thanks to a gynaecological oncologist in Belgium who has made cancer in pregnancy his specialist field. As a result, his group – and those in other centres following his research – are now routinely able to not only save the life of the baby but also avoid compromising the mother's chances of surviving.

Most oncologists work in cancer because of the potential to save lives. Rare is the doctor who gets the chance to save two lives at the same time, as with cancer in pregnancy. That is because it is not common – about 1 in 1,000–2,000 women will be diagnosed while pregnant, although exact figures are not available. "Obstetric and cancer registries are separate, so no one really knows the full pregnancy connection," says Frédéric Amant, head of gynaecological

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oncology at Leuven, and the doctor in question. "But with women in western countries having children later in life, there is likely to have been a rising incidence."

Given that there are about 5 million babies born each year in Europe, there could still be some 2,500–5,000 cases of pregnant women with cancer, with each potentially demanding a complex intervention from a wide range of professionals, from obs/gyn, medical oncologists, surgeons and counsellors, to the logistics of managing patients who would prefer to be at home.

All this used to be of purely academic interest, as treating a pregnant woman with chemotherapy has only recently become a standard option. "It was in 2002, after I had completed my PhD, that I started looking at new research options and I was confronted with a patient with cervical cancer who was 15 weeks pregnant. The standard treatment was abandoning the pregnancy and carrying out a hysterectomy. But she had lost a previous baby owing to premature labour, and this was her last chance. We explored the literature in a bid to save both lives."

Amant gave the woman chemotherapy, and she went on to have a healthy baby and both are doing well today. "We knew that others had given chemotherapy for a range of cancers –

It turns out that the placenta is excellent at protecting the foetus from the commonly used breast cancer drugs

breast being the most common in women of childbearing age – and that there was anecdotal evidence that babies were not harmed. But there were so many unanswered questions, and I decided then that this would be an area I could explore systematically and prospectively to really make a big difference personally, rather than playing a minor role in much larger fields such as breast and ovarian cancer research."

In just over ten years, Amant and colleagues have filled in much of the missing information and have paved the way for treating pregnant women with cancer. The most important question is about harm to the foetus, and whether there are later effects as a child grows up, which clearly takes time to answer, and research is ongoing. The results so far show little or no harm. "The reason that is the key question is that, if it is shown that chemotherapy is detrimental to the foetus, then other research becomes unnecessary. But now we have answered basic questions on foetal safety, we have also turned to other important questions such as maternal safety, as there was a belief that women had better chances if they had an abortion before treatment. But again, this is not the case," says Amant.

"Initially, though, it was hard to get grants to do this work, as funders just didn't think it was realistic. Even the powers here at Leuven didn't believe in it at first."

He set about publishing in high-impact journals to raise the profile of the subject, and has now succeeded in establishing an impressive body of work with colleagues, including the world's largest database of pregnant women with cancer, which is maintained at Leuven on behalf of the International Network on Cancer, Infertility and Pregnancy (INCIP).

Consensus guidelines for treating breast and endometrial/cervical cancers are now in existence, with haematological guidelines in preparation. A cohort of children born to women with cancer is being followed up, and a website, cancerinpregnancy.org, details and publicises the work, which also has cross-over into other research on younger women, such as preserving fertility. A key step, says Amant, was recruiting a communications and fundraising officer, Griet Van der Perre, to attract resources, in addition to support from the university.

But not all women, even in western healthcare settings, are yet being offered the chance to undergo treatment without a termination, says Amant. There are organisational obstacles – a smaller hospital may not have the multidisciplinary team needed, or may be unaware of a referral option to a centre such as Leuven. Like many rare cancer conditions, much often depends on a doctor being motivated to read the research and act on it, and there may be a lack of awareness even in larger centres.

"At a meeting last year in Paris I had an oncologist approach me from a large French centre saying he wasn't up to speed on our findings," says Amant. "We've had a young researcher from Italy working with us who would have liked to introduce the work when she returned home, but her boss took it over and then was too busy to do it. I even had a call from a journalist in New York who had cancer when pregnant whose doctors didn't want to treat her until she showed them our research."

Put bluntly, there are women now having unnecessary abortions in many countries – and Amant has a firm ethical stance that where the science shows that treatment is safe he will not perform an abortion if asked. "It does happen that a woman will ask for a termination against our recommendation – but she has to go elsewhere, as is her right. This is not a religious standpoint but an ethical respect for life – in one case a woman with breast cancer and a baby that was almost viable at 23 weeks did ask us to perform an abortion but I said, 'Your

baby has a right to live.' Sadly she went to another hospital to have a termination."

The key is confidence in the robustness of the science. Amant admits that at the start there were doubts. "Our counselling used to be less definite. There are also wider issues to consider, such as the views of the woman's partner, who could be left to bring up a child if the mother dies, and of course there are women who have advanced cancer, where it is often best to have a termination, or decide to go ahead anyway knowing they will die, and there can be heartbreaking meetings."

But now, for women with say early-stage breast cancer, Amant and colleagues are able to lay out the evidence that surgery, and chemotherapy and radiotherapy if needed, can proceed more or less the same as if the woman was not pregnant, alongside the ethical considerations of saving the baby's life.

"I used to spend an hour or so in outpatient meetings to explain the options. Now it takes 15 minutes. I used to also go to the labour ward to check the baby was normal after delivery. Now I don't need to. This is confidence in our work, and of course ensuring that patients trust it." He uses the term 'paradigm shift' to describe the change in practice, a term not to be used lightly, and which won't be proven until it is truly universal across healthcare systems.

The research on chemotherapy and the foetus comes partly from animal studies, in particular on baboons, which have a placenta that behaves in a similar way to a human placenta. Chemotherapy and indeed some targeted agents such as trastuzumab (Herceptin) had been given to pregnant women before the new research, but it was simply not ethical or safe to do this, says Amant.

The first point to note is that chemotherapy is not given in the first trimester, when the foetus is most vulnerable. It turns out, however, that the placenta, which offers little defence against substances such as alcohol, viruses and bacteria, is excellent at protecting the foetus from taxanes and anthracyclines, classes of drugs that are commonly used in breast cancer. "Only 1% and 5% respectively of these drugs are detected in the foetus compared with the blood level in the woman's own circulation," says Amant. "In fact all cytotoxic drugs are found in lower levels in the foetus, and some taxanes are actually undetectable, although other drugs have higher levels, such as carboplatin at 60%."

Antibody drugs are more of a problem, and targeted therapies such as trastuzumab should not be given. Amant says that where trastuzumab has been tried it affects HER2 receptors in the kidneys of the foetus. This can result in potentially life-threatening respiratory problems for the newborn child, because it leads to the foetus producing less urine, which in turn reduces the amniotic fluid which the lungs need to inhale in order to develop. Not giving trastuzumab is, therefore, one of few variations in standard therapy that a woman with early-stage invasive breast cancer can receive when pregnant (although hormone therapies should also be avoided until after birth).

There is time to plan drug treatment in the month after the first trimester, starting at 12–14 weeks

Breast cancer accounts for about 40% of instances of cancer in pregnancy (as with non-pregnant younger women), followed by haematological cancers at about 11%, and then cervical cancer where, although surgery is often not an option, neoadjuvant chemotherapy is.

Amant dispels other beliefs. "It was thought that pregnancy stimulates cancer and makes it more aggressive – but the prognosis is the same as for non-pregnant women with the same grade of tumour," he says, though he adds that breast cancer is often diagnosed at a later stage in pregnant women because changes in the breast can disguise lumps.

He also points out that being diagnosed with breast cancer in pregnancy is not an emergency, and there is time to plan drug treatment in the month after the first trimester, starting at 12–14 weeks (surgery can be carried out earlier).

There is some concern, however, about women who are diagnosed in the first year after giving birth (the incidence is similar to breast cancer in pregnancy), who are generally known to have worse outcomes than the general population of women with breast cancer. The reasons are the subject of current research and part of a spectrum of work that Amant and colleagues are engaged in on younger women.

Allied research includes investigating whether breast cancer raises the risk of a recurrence if a woman becomes pregnant (the evidence so far says not), and exploring the incidence of becoming pregnant during cancer staging or treatment, which seems to be around 3%, prompting calls for oncologists to discuss contraception with their patients, in addition to fertility.

It is the variation in obstetrics and gynaecology that drew Amant in. "I fell in love with it as a student and decided on it after being at my first caesarean section. Just surgery was too narrow – in obs/gyn I realised I could also do everything from endocrinology to fertility to cancer. I became particularly interested in cancer because, while not trivialising all the other complaints that women often have, they really do have major physical and emotional problems with cancer, and I had a lot of empathy with them and felt it would be a field that would have my interest for many years."

Amant, who trained at Leuven, wanted a post in gynaecological oncology there but was told there wasn't one, so went with his family to Pretoria, South Africa to do an oncology fellowship with no promise of a job on his return. "I then got a call from Leuven offering me a post – it was because they saw how motivated I was." For his PhD he started on his goal of selecting research in neglected areas by looking at uterine sarcomas, and went on to qualify as one of Belgium's first gynaecological oncologists, accredited by the European Society of Gynaecological Oncology (ESGO).

Since then he has also established himself as an expert in endometrial cancer, which is the most common gynaecological tumour and has a good prognosis, but again has been neglected. He chairs the EORTC's endometrium committee, and is the current chair of INCIP (International Network on Cancer, Infertility and Pregnancy), but has chosen not to pursue the presidency of ESGO or other larger societies – "I'm not a meetings person and I feel I can have more impact at Leuven," he says.

At Leuven, he has also established a platform for researchers in other cancers, with a new type of mouse model that uses patient-derived tumour xenografts – implanting human biopsies in mice provides an *in vivo* model that is more clinically relevant than using

cultured cell lines. "Essentially, we are cloning the patient's tissue in mice. Once a drug proves effective in mice, the success rate in a patient with the same genetic characteristics is much higher, and my group coordinates a xenograft service for nine tumour types so far at Leuven," he says.

That group is now 18 strong, and is rolling out more research, and also running events such as the recent International Symposium on Cancer in Young Women, held last February in Leuven, which divided into a day on cancer in pregnancy, and a day on topics such as fertility preservation, ovarian damage from treatment, pregnancy after breast cancer and uterus transplantation.

Amant's group is also involved with, or follows closely research on, mainstream breast, ovarian, cervical and others. There is still a lot to do in cervical cancer screening, where only 60% of Belgian women are in the national programme, he notes.

He is optimistic that the early results from the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS), a study of 200,000 women that has recently reported that testing the CA125 blood marker could detect twice as many women with ovarian cancer, will lead to a better outcome for this major killer.

The size of this study in sheer patient numbers highlights the difficulties in assessing outcomes in the far smaller numbers of women and children involved with cancer and pregnancy. That's why, says Amant, the Leuven registry includes a control of non-pregnant younger women who have had breast cancer along with those who had cancer during pregnancy.

This is where the results showing that survival rates are similar in both groups have come from, although there are limitations, as pregnancy data has been retrospectively pooled from hospitals in several countries, but the control is from one hospital, and there is only sparse information on factors such as family history of breast cancer. But Amant says it is much better than previous studies (see *JCO* 2013, 31:2532–40).

He accepts that lack of a control has been a valid criticism of follow-up work on children born to women with cancer, which may explain why some oncologists have so far been reluctant to recommend treatment. The published work is an observational study on the long-term cognitive and cardiac outcome after chemotherapy exposure (see *Lancet Onc* 2012, 13: 256–264).

Importantly, this study identified that children born prematurely do have associated cognitive impairment, so a key message is that there should not be a policy for early delivery, as has been previously recommended. "We have shown that babies suffer more from prematurity than they do from chemotherapy," says Amant.

In this multicentre study, 70 children between one and 18 years underwent evaluations, with normal cognitive development seen in the majority. And there was no association with heart abnormalities. "A control group is the best way to improve the research," says Amant, who says that a case control study is underway. Early results were presented at ESMO last year, comparing 38 children with controls, but it needs to be published in a high-impact journal to take hold. His group is also carrying out follow-up work on children whose mothers were exposed to radiotherapy during treatment.

There is a challenge, though, in convincing older children, especially teenagers, to take an interest in the research "We do send them a

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Two lives protected. Lesley Verley is one of a growing number of women who have been treated at Leuven hospital with chemotherapy while pregnant; she is pictured here with husband Andy and newborn baby Marnix – now a healthy 5-year-old

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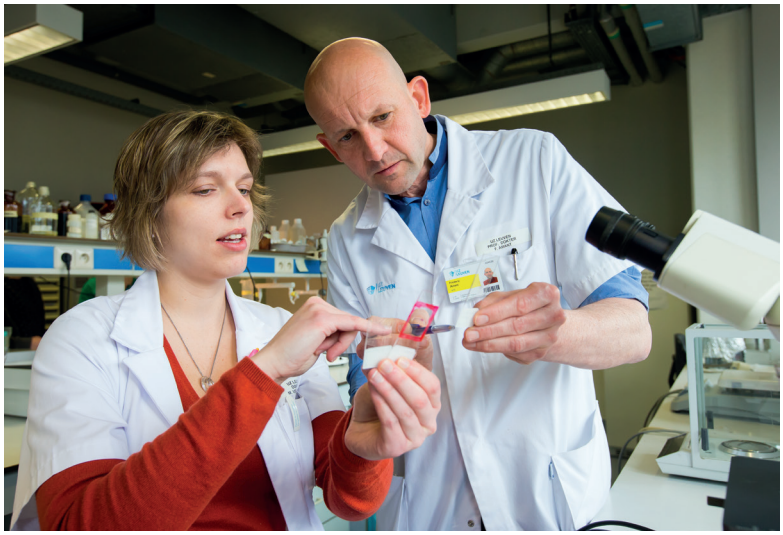

birthday card and we also hold a family day to link people in the project."

Another way of refining the research – and dependent on larger numbers and robust follow-up – is determining whether one type of chemotherapy could be responsible for certain harms. The current study pools all chemotherapies and is not large enough to draw conclusions on classes of drug, says Amant. "It may be that some are more toxic. There is a case report, for example, on cisplatin being associated with hearing problems. We also have only small numbers of children whose mothers received carboplatin, which does have higher levels in the foetus." At present, centres in the Czech Republic, Italy and the Netherlands are collaborating on such child follow-up studies with Leuven.

Given the small numbers – Leuven treats just ten women a year but gives advice to other hospitals – it is vital that more national and international collaboration takes place, adds Amant, but as other centres become confident in treating their own patients, more could be lost from Leuven's network of referrals and advice and its database, which is not good for the research. Also a potential confounder is the increasing use of targeted therapies, which could convince more women to terminate pregnancies in favour of new treatments.

That would be a shame, given the evidence that Amant's group continues to build. For example, his colleague Sileny Han has found that a sentinel node biopsy used instead of full lymph node dissection to stage breast cancer is just as applicable to pregnant women. "There are two issues – the foetus is not put at risk by the radioactive tracer used in the sentinel node procedure, and there was a concern that, with changes in a woman's lymphatic system during pregnancy, we might find more false-negatives. But follow-up has shown we don't see any more cancer recurrences, which we would if there were more false-negatives." He adds that Han, together with radiologist Vincent Vandecaveye, has also been looking at the use of whole-body MRI scans to see if they are detailed enough to show cancer sites in pregnant women.

But there are also women who have read about Amant's work and contact Leuven to take part in the research, notably Caroline Swain in the UK who was diagnosed with breast cancer when pregnant with her second son. There is a documentary and articles about her and her family at cancerinpregnancy.org.

More broadly, there is a concern that pregnancy is an understudied part of medicine from the point of view of other treatments, not just for cancer. Amant is on the advisory board of the Pregnancy and Medicine Initiative, which notes that "medical care during pregnancy is lacking proper data and approximately 90% of pregnant women take medicine without knowing the consequences."

Meanwhile a constant stream of media news stories on mothers treated for cancer during pregnancy from around the world show that there is still much to do in embedding this work in practice. A mark of progress may well be when these stories are no longer deemed newsworthy. ■