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de Haan, J.

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CHAPTER 10

General discussion

As defined by the WHO, a disease is considered rare if the number of affected people is less than 5 per 10 000.¹ The care for patients with a rare disease is complicated by fundamentally different challenges compared to patients with more common diseases. The small number of patients, lack of validated diagnostic and treatment options, logistic problems due to scattering of these patients across countries, and limited clinical expertise are only some of these challenges. With this fragmented disease knowledge, international networks are critical to develop well-organized research, adequate infrastructures and training of health professionals.¹

Over the years, several nationwide population studies performed in Western countries estimated the incidence of cancer in pregnancy on 1 in 1000 live births.²⁻⁴ In the Netherlands, with an average of just over 170 000 live births annually in the last 5 years⁵, this translates to approximately 170 pregnant women diagnosed with cancer every year. With 1000 gynaecologists working in 91 hospitals in the Netherlands^{6,7}, each gynaecologist will see 0.17 of these patients per year, resulting in an average of not even two patients per hospital per year. This number is even lower if the different malignancies that can occur during pregnancy are taken into account. Although cancer in pregnancy overall does not meet the official WHO criteria of a rare disease, the subgroups based on malignancy type do. Also, the unique situation of cancer during pregnancy encounters the same problems described above for rare diseases. This confirms that cancer in pregnancy should be regarded as a rare disease.

It is widely accepted that exposure of a medical specialist to a rare health problem, is related to knowledge and quality of care. This is why the Dutch Foundation on Oncological Collaboration (Stichting Oncologische Samenwerking, SONCOS) defined minimal requirements for oncologic care in order to pursue optimal care for cancer patients.⁸ These requirements include an experienced multidisciplinary team including a case manager, presence of facilities needed for malignancy specific optimal care, participation in clinical trials and national registrations to evaluate quality of care and a minimum number of patients with a specific malignancy (for less common malignancies a minimum of 10 per year).⁸ Such guidelines and requirements have not (yet) been developed for cancer in pregnancy, but are necessary in the near future. In this discussion we will further elaborate on the changes in the management of cancer in pregnancy in the past up to the present situation and will discuss the needs for the future.

PAST

Awareness that cancer in pregnancy occurs and requires specific (multidisciplinary) expertise is growing the last decade, but was limited before 2005. Before 2005, a European registry on cancer in pregnancy was lacking, literature was scarce and knowledge was scattered. Realization of this lack in health care resulted in establishment of the registration study on cancer in pregnancy in Leuven, Belgium. Over the years, the small group of participants expanded into international collaborations with a variety of medical specialists, resulting in the international taskforce on cancer in pregnancy and later in the International network on Cancer, Infertility and Pregnancy (INCIP). With the primary objective to register patients with cancer in pregnancy to increase knowledge, the number of patients included in this study continued to increase resulting in 1732 patients to date, and 20 years of unique data. As shown by this thesis, the number of patients receiving oncological treatment during pregnancy increased in the last 20 years (10%, every 5 years), which is mainly due to increasing numbers of chemotherapy exposure (31%, every 5 years). Also, every 5 years, we observed more live births (4%) and fewer iatrogenic preterm deliveries (9%).

Even though this cohort is the largest to date and one-of-a-kind, results of this study are based on a voluntary registration which, by definition, leads to underreporting and selection bias. In our opinion, and in line with the SONCOS requirements for good oncological care, registration of these patients should be obligatory, not only since we are obliged to evaluate our own provided care, but also because we have a moral obligation to continue to improve the care for these patients and their unborn children.

PRESENT

Personalized care and shared decision making

Tailor made medicine in oncological care is a rapidly growing approach where, based on malignancy specific characteristics, individualised treatment regimens are given. However, malignancy specific characteristics are not enough to provide tailor made care. Patient specific characteristics are equally important to consider for a specific treatment. A pregnant patient has her unique social situation, personal beliefs and own preferences which can only become comprehensible after a process of shared decision making. The outcome of this process is as important for the tailor made care as the malignancy specific characteristics. Management of all cancer patients should involve an experienced multidisciplinary team.⁸ This is even more important for pregnant cancer patients, as management not only includes the oncological management that is best for the patient herself, but also includes her unborn child. Additionally, the psychological burden will be

different in this unique situation, for both patient and her family. Besides including the same healthcare professionals as for non-pregnant cancer patients, specialists to provide the best obstetric and neonatal care should be included. This will result in a rather large team covering all facets, as displayed in Figure 1.

Maternal benefits and fetal safety continuously needs to be balanced by this multidisciplinary team. Optimal care for one may not benefit the other, with a risk of suboptimal oncologic treatment regimens and adverse obstetrical and neonatal outcome, like preterm birth, small for gestational age (SGA) or neonatal intensive care unit (NICU) admission.⁹⁻¹⁹ We confirmed these adverse outcomes in our cohort of 1170 pregnant patients with a primary malignancy from the INCIP registration study and were able to identify specific risk factors associated with these adverse outcomes. Platinum-based chemotherapy was associated with small for gestational age neonates and taxane chemotherapy was related to NICU admission.

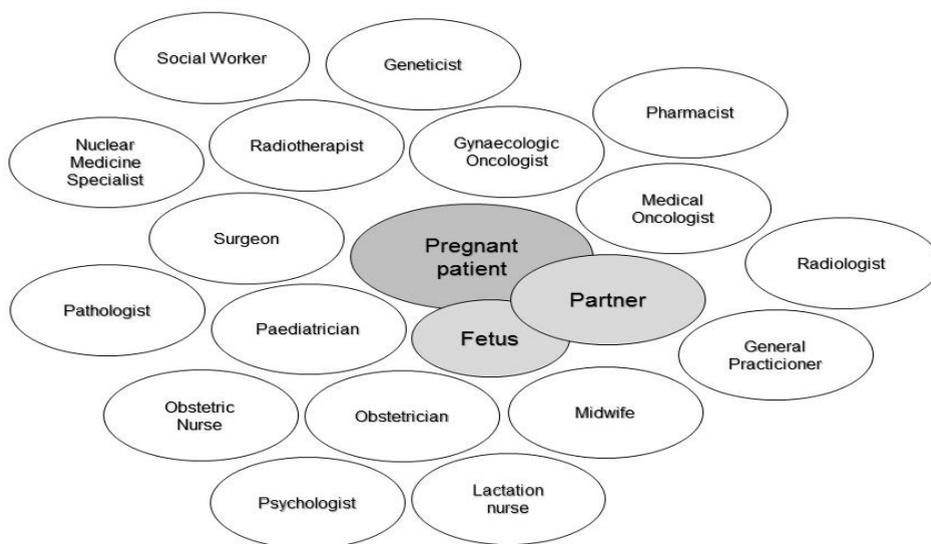


Figure 1. Overview of specialities and experts potentially involved in the management of pregnant cancer patients.

Over the years, several studies have reported on the fetal safety of antenatal oncological treatment with reassuring results on paediatric development.^{12,17,20,21} And even though antenatal chemotherapy exposure is associated with small for gestational age neonates and NICU admission, follow-up to the age of three has shown no difference

regarding general health, neuropsychological- and cardiac development in these children compared to children born from healthy controls.¹² The main predictor for adverse paediatric outcome was preterm birth in both groups, stressing even more the need to explore the possibilities of antenatal oncological management to postpone delivery. While these results probably have strengthened healthcare professionals and patients in the decision to start antenatal chemotherapy, little is still known about the long term effects of antenatal chemotherapy exposure. For example, gonadotoxic effects of chemotherapy on the non-replenishable pool of follicles in girls after antenatal chemotherapy has never been reported. Chemotherapy may negatively affect ovarian function, because this was also reported after chemotherapy exposure during childhood.²² In childhood cancer survivors, reduced ovarian function was associated with high doses of alkylating agents²². Alkylating agents are the second most administered chemotherapeutic agents during pregnancy and placenta passage is up to 20% of the maternal concentration.²³ As fetal metabolism differs from children and exposure dose depends on the maternal dose and number of cycles, we cannot estimate if fetal exposure to alkylating agents in our population should be considered as high dose. Another risk factor for reduced ovarian function was older age at treatment, which could be favourable for antenatally exposed girls.²² Long-term follow-up of these children, and not only girls, is essential to answer these and other clinically relevant questions.

The INCIP has created a platform to collect data and to answer such questions in the future. But further steps are necessary to influence the actual care of this rare patient population in both The Netherlands and in Europe. Currently, the European community is supporting the establishment of reference networks which should improve care for patients with rare diseases. European Reference Networks (ERNs) are virtual networks of healthcare professionals in Europe, with the goal to provide patients with rare diseases specialized treatment in expert centres. One of the networks is the European network for rare adult solid cancer (EURACAN), which aims to share 'best practice' guidelines and to establish referral hospitals to support optimal treatment and to improve prognosis. Unfortunately, the INCIP could not participate in this network due to the patient population, which does not cover one specific solid malignancy. However, the INCIP has enough potential to become an ERN on its own, or even an International Reference Network (IRN). In the Netherlands, a first step in realizing a national reference network has been made in 2012, when the national Advisory board on Cancer in Pregnancy was established. This advisory board consists of healthcare professionals from different hospitals and covers most of the specialisms involved in the care of pregnant cancer patients. All these professionals have their own expertise in the

treatment of these patients and are available per e-mail for consultation by other healthcare professionals confronted with a pregnant patient with cancer. The aim of this advisory board is to advise patients and healthcare professionals on optimal tailor made care, based on up-to-date information about the possibilities and risks of diagnostics and treatment. The board will advise referral to another hospital if specific expertise is required and aims to include these patients into the ongoing INCIP research projects. Even for dedicated specialists it is a challenge to get experience with all different malignancies in different stages of disease, certain gestational ages and other obstetrical comorbidities. In the Netherlands, the advisory board is receiving a growing number of consultations every year, from two in 2012 to 28 in 2018. Such an increase in patients is also seen in the INCIP registration study (Figure 2), probably due to more awareness of centralized knowledge and the existence of this study. However, with these numbers the exposure to patients with cancer during pregnancy remains rare and international collaboration remains of uttermost importance. We believe national advisory boards are key in aiding future collaboration within Europe and the rest of the world.

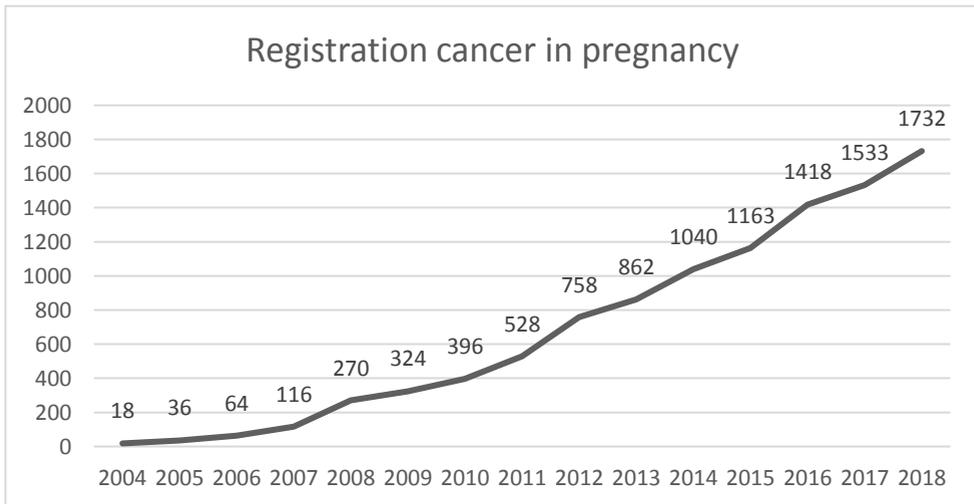


Figure 2. Overview of the number of included patients in the INCIP registration study, updated August 2018.

FUTURE

Research answers questions, but it also generates new ones and shows opportunities for improvement. One of the most important questions is “how can we further improve outcome and individualized counselling for all pregnant cancer patients and their children?”. Since oncological care has many facets and our population is heterogeneous in patient characteristics and logistically scattered, a simple answer is impossible to give. In the future we need to investigate the specific needs of this patient group, the best way to organize care, further increase awareness and how to integrate modern social media possibilities in the care of patients.

Individualized medical care

Individualized care starts by identifying the individual needs of the patients. Even though these needs are different per patient, several generic subjects can be identified from the care for non-pregnant cancer patients, like quick and accurate diagnosis, up-to-date treatment to improve prognosis, optimal routing, psychological guidance and clear communication. Although the primary oncological needs for our patients are comparable to non-pregnant patients, an additional and different level of needs arise due to the presence of the unborn child. As discussed in this thesis, evaluation of new diagnostic tools and assessing its accuracy and safety during pregnancy are important, as it can reduce delay in diagnosis and has the opportunity to improve maternal outcome. Evaluation of new therapeutic options can be more difficult. All medical trials exclude pregnant patients and counselling of patients can only be done based on theoretical risks, risks proven in animal studies or by reported cases in literature. The only way to evaluate the safety of these new therapies is by registration of those patients who underwent them. This is where the INCIP network comes in once again. We want to emphasize the need to register even more when discussing these new developments, as it is the only way to research potentially lifesaving interventions during pregnancy. With such a fast evolving field as oncological medicine, subgroups with specific (research) questions will always arise, making the INCIP registration study continuously important in providing mother and child with the best possible care and counselling.

Individualized psychological care

Concerns of patients and healthcare professionals for adverse obstetrical outcome are specific for the patients with cancer in pregnancy. Research projects to investigate these concerns and the possibilities to handle them are essential. The needs and concerns are

different during the process of diagnosis and treatment, during pregnancy or after termination or delivery. Exploration on these phase-specific needs by, for example, research project with a short questionnaire at different moments in the process could identify them. This could further lead to validated questionnaires to early identify those patients in need of additional guidance. Vandenbrouke et al. started such a research project to identify psychological distress and coping strategies of patients and their partners to identify those in need of additional psychological support.²⁴ For example, they found that patients were more inclined to maintain pregnancy compared to their partners. Also, both patients and partner who used internalizing coping strategies experienced more distress concerning the child's health, disease and treatment, and pregnancy and delivery. Early identification of these patients can provide early (psychological) support. Other potential subjects for counselling are for example family support, breast feeding, dietary or work advice. The possibilities of providing such support is rapidly growing with the development of video consultations, telephone applications and group pages on social media. These new ways of support can be helpful to improve care in the future even more.

Centralized care

Care for pregnant cancer patients should always include an experienced multidisciplinary team. Figure 2 describes the ideal team of caregivers that should be involved in the care of a pregnant patient with cancer. It is not very advantageous to establish such a team in every hospital. In these days, where cost-effectiveness is very important, creating a team of medical specialist for two patients each year is not opportune. A specialised team in only a selected number of hospitals will aid both the efficiency and efficacy. Therefore, centralization to a certain extend in the future seems only logical. Medical care, and especially oncological care, is expensive and will probably become even more expensive as new therapies become available. This demands a for continuous and critical evaluation of logistics and care, in order to construct a long-lasting and sustainable network. Depending on the incidence of the malignancy and the treatment required during pregnancy, the number of hospitals specializing in these pregnant patients should be calculated using the SONCOS criteria as mentioned above. For example, this could result in seven hospitals specializing in breast cancer during pregnancy but only one hospital specializing in colorectal cancer during pregnancy in the Netherlands. For those extremely rare malignancy types, international specialized centre could be the solution.

When different levels of care are given by multiple healthcare professionals in potentially different hospitals, the key in continuous care is having one case manager. Since

the intensity of oncological and obstetrical care needed will differ per patient based on malignancy, stage of disease and type of therapy needed, the exact routing of care will differ per patient as well. The decision on which patient should be treated where needs to be done by a multidisciplinary team in a specialized centre. We strongly recommend to have one case manager for every patient, preferably in the hospital where the patient plans to deliver, since the obstetrician is the central healthcare professional for all these patients.

Advisory Boards and International Collaboration

The need for different levels of specialized care depends on malignancy type, the required diagnostics and treatment, gestational age at diagnosis or treatment and choices of the patient after counselling. Aside from hospitals for specialized care, a nationwide advisory board on cancer in pregnancy, as has been established in the Netherlands, can assist healthcare professionals and patients with gathering accurate information about the optimal management. We plea for a nationwide advisory board on cancer in pregnancy in every country in Europe, which should be an easy assessable resource for local doctors when confronted with a pregnant patient with cancer, and also facilitates international collaboration when facing rare or complex situations. Ideally, every consultation is answered within a short period of time, should contain up-to-date and practical information and must be based on national and international guidelines. At an international level, the challenge is even bigger. In order to achieve an international consultation possibility, we propose several options:

1) Establishment of international subadvisory boards on specific malignancies. For example, a request for a consultation can be placed on a website hosted by INCIP. Questions must be divided by speciality and malignancy type, making it possible to directly send the appropriate question to the specialised subadvisory board. This subadvisory board can consist specialists on specific subjects from national advisory boards. This way specific questions are only asked to those with the most knowledge, resulting in the most specialised answered and lowering work load for the other members of the advisory board.

2) A website containing a digital version of all available guidelines and the 'Textbook of Cancer in Pregnancy' with background information (published by ESGO in 2017)²⁵, can aid both healthcare professionals and patients. Keeping such a website up-to-date is time-consuming. It should be maintained by one or two moderators that also initiate the regular update of guidelines by, for example, planning (online) consensus meetings. Links to research projects, specialised referral hospitals per country and to the consultation request page could also be placed on such a website, combining everything on one place.

3) Yearly (consensus) meetings in changing countries. This can aid the establishment of up-to-date and experience based guidelines. Also, these meetings can be used to discuss results of and improve participation to these projects and to improve collaboration.

4) Educational programmes for healthcare professionals. For example by hosting a yearly course on cancer in pregnancy with state of the art lectures on different levels of care. Also, a possibility of participating in an e-learning or interactive online course could provide international professionals with easy accessible knowledge leading to improved care and possible improved outcome.

Increasing awareness

Key in improving maternal and neonatal outcome is awareness on the occurrence of cancer in pregnancy and the possibilities and risks of management. As the INCIP is growing, in both participating healthcare professionals and published research, awareness is growing as well. It continues to be important to spread the message and to include patients in research projects. Unfortunately, not all countries and specializations are represented equally in the INCIP. Not only healthcare professionals specialized in the care for oncological patients should be involved in the INCIP and research but also general practitioners and midwives should participate as they will see the patients with complains for the first time. Also, awareness by potential patients must be increased so they will not ignore possible symptoms and seek help earlier in the process. By further expanding our research projects, presenting on international congresses for different disciplines and involving national and international media we aim to improve awareness and increase further participation in essential research projects.

Future research perspectives

Most of the research in this thesis is based on data from the voluntary registration study of the INCIP network. We already discussed the pitfalls of such a voluntary registration, leading to an underestimation of the prevalence and possibly the adverse outcome. Due to underreporting of patients, subgroups of lesser common malignancies become even smaller resulting in difficult to interpreted results, as shown by the subgroup analyses published in this thesis on thyroid cancer, colorectal cancer and melanoma. In these studies, maternal follow-up is relatively short and is lacking data. Effects on obstetrical and neonatal outcome of specific therapies in these patients, let alone the effect on maternal outcome, are very difficult to analyse, resulting in descriptive analysis only. Especially when

new immune- or targeted therapies are the only option for maternal treatment, as was the case in our case report on advanced stage disease melanoma, sharing the maternal and fetal outcome with other medical specialists is indispensable. Currently, these novel therapies must be used only in pregnancy when other treatment options are lacking and close evaluation of maternal and fetal short- and long term wellbeing is monitored. Obligatory registration and centralization would further facilitate this registration and is the only way to better handle these rare and complex situations in the future. Additionally, we plea for anonymous linkage between nation- and European wide databases such as national cancer registries, birth registries, death registries and possibly even pathological registries, to reduce selection bias to almost zero. With new European laws on protection of privacy data introduced in 2018, this goal has become more difficult to achieve, making active participation of patients and healthcare professionals to our research projects even more essential.

In the end, we all aim for the best care and outcome of our patients. A question that we must always ask ourselves is: **“do we have all the expertise needed for the best possible care and if not, do we consult to gain that expertise or should we refer our patient”**. As mentioned above, it is unrealistic to have an experienced multidisciplinary team in all hospitals in the Netherlands. We therefore owe it to our patients and ourselves to invest in centralizing care by constructing specialized referral hospitals, by centralizing knowledge both nationally and internationally and by further expanding our research with mandatory (online) registration. With such a vision in a structured network of dedicated healthcare professional and researchers, the number of adverse outcome for both mother and child will hopefully be reduced even more in the future.

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