# Childbearing after hyperthermic intraperitoneal chemotherapy: results from an international survey.

Pablo Ortega-Deballon, Olivier Glehen, Edward Levine, Pompiliu Piso, Paul Sugarbaker, Andrea Hayes-Jordan, Audrey Facy, Naoual Bakrin, Patrick Rat

# Childbearing after hyperthermic intraperitoneal chemotherapy: results from an international survey

Pablo Ortega-Deballon[1,2], Olivier Glehen[3], Edward Levine [4], Pompiliu Piso[5], Paul H Sugarbaker[6], Andrea Hayes-Jordan[7], Audrey Facy[2], Naoual Bakrin[3], Patrick Rat [1,2]

[1] *INSERM UMR 866, Dijon, France.*

[2]*University Hospital of Dijon, Dijon, France*

[3] *University Hospital of Lyon South, Pierre Bénite, France*

[4] *Wake Forest University Baptist Medical Center, Winston-Salem, NC, USA*

[5] *University Medical Center of Regensburg, Regensburg, Germany*

[6] *Washington Cancer Institute, Washington, DC, USA*

[7] *MD Anderson Cancer Center, Houston, USA*

**Corresponding author and reprints**:

Dr Pablo Ortega Deballon
Service de Chirurgie Digestive, Thoracique et Cancérologique
Centre Hospitalier Universitaire du Bocage
1, Bd. Jeanne d'Arc
21079 DIJON Cedex, France
e-mail: pablo.ortega-deballon@chu-dijon.fr
Tel. +33 380 29 37 47
Fax. +33 380 29 35 91

This work was supported by a grant from the University Hospital of Dijon and the Regional Council of Burgundy 2009.
No other commercial sponsorship or conflict of interest declared.

**Running title**: Childbearing after HIPEC

**Synopsis**: This international survey collects information about pregnancies in women having undergone previous cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for peritoneal malignancy.

**ABSTRACT**

**Background.** Cytoreductive surgery (CRS) and heated intraperitoneal chemotherapy (HIPEC) can improve survival in selected patients with primary or secondary peritoneal malignancies. With the opportunity for long-term survival, questions about the impact of those procedures in fertility in women of childbearing age can be raised.

**Methods.** An international survey was performed among all teams participating in the International Peritoneal Surface Malignancy Group in order to collect data about pregnancies and their outcome in women having undergone previous CRS with adjuvant HIPEC.

**Results.** Seven pregnancies were reported after CRS and HIPEC in women treated for peritoneal malignancies. All these women conceived spontaneously, most of them within 2 years after the procedure. They delivered most often by vaginal way after an uneventful pregnancy. Their newborns were healthy, except one case of congenital diaphragmatic hernia requiring emergent surgery. Two additional uneventful pregnancies were reported after the diagnosis of pseudomyxoma peritonei and before CRS and HIPEC, with the support of the medical team. Another woman having undergone oocytes retrieval and embryo cryopreservation prior to the surgery was mother of twins after the procedure via a surrogate mother.

**Conclusion**. Childbearing after cytoreductive surgery and heated intraperitoneal chemotherapy is possible in women conserving their genital organs after the procedure. The question of fertility should be considered and discussed in women in reproductive age prior to cytoreductive surgery and heated intraperitoneal chemotherapy. Different options could be offered in this setting. Multidisciplinary decision making involving surgical oncologists and fertility specialists is important.

## INTRODUCTION

Cytoreductive surgery (CRS) followed by heated intraperitoneal chemotherapy (HIPEC) is increasingly accepted as the best therapeutic option in some primary or secondary peritoneal malignancies. These procedures result in improved and even long-term survival in patients with peritoneal carcinomatosis from colorectal origin, pseudomyxoma peritonei and peritoneal mesothelioma [1-4].

Peritoneal carcinomatosis from colorectal origin is not frequent among women in childbearing age group. It is more common to find young women with pseudomyxoma peritonei (PMP), peritoneal mesothelioma, ovarian or appendiceal tumours undergoing HIPEC. During CRS for primary or secondary peritoneal neoplasms, an extensive peritonectomy is usually performed, with subsequent postoperative adhesions and impaired tubal motility. Moreover, the uterus and ovaries are often removed during the procedure. Even when they can be conserved, they are bathed into hyperthermic chemotherapy during 30 to 120 minutes [5-7].

With the opportunity for long-term survival, the question of fertility and prognosis of pregnancy may be raised and no data are available in the literature to inform patients regarding these issues.

The aim of this international survey was to record pregnancies in women having undergone a previous CRS and HIPEC. Secondarily, we tried to collect information about delivery issues, health of the newborns and fertility.

## METHODS

A questionnaire was sent to all surgical teams participating in the International Group on Peritoneal Surface Malignancies. Overall, the questionnaire was sent to 79 teams in the world that are involved in the management of peritoneal surface malignancies and are routinely performing the combined treatment (CRS and HIPEC). They were asked to answer if they had any case of pregnancy or miscarriage after CRS and HIPEC and to fill in a detailed questionnaire in case of positive answer.

The questionnaire recorded data about the disease (type of disease, Sugarbaker's Peritoneal Carcinomatosis Index [8]), technical aspects of CRS and HIPEC (type of cytoreduction achieved (Table 1) [9], ovarian and uterine conservation, chemotherapy used, duration of HIPEC, temperature achieved, maximal temperature reached during HIPEC), previous childbearing history, data regarding pregnancy after HIPEC (interval between HIPEC and pregnancy, age of the patient, need for assisted medical procreation and type of techniques, follow-up of pregnancy and data regarding delivery and newborn health status), and data regarding the follow-up of the neoplasm.

The protocol was approved by the national french authorities regulating confidentiality and ethics in medical research (CCTIRS, number 09475; and CNIL, authorization number 909458).

This work was supported by a grant from the University Hospital of Dijon and the Regional Council of Burgundy 2009. This grant financed sending the questionnaire and the administrative costs of submission for ethics and for the national regulatory organism regarding confidentiality of data in medical research. No other commercial sponsorship or conflict of interest declared.

## RESULTS

Seven pregnancies were reported in women having undergone previous CRS and HIPEC, with delivery of seven newborns (description of these patients in Tables 2 and 3). All these women had undergone genital organs-preserving CRS (only patient 3 had right oophorectomy during surgery). Five of them were treated for PMP and two for peritoneal mesothelioma; they were all disease-free at the end of the follow-up. Patient number 2 received a GnRH analogue prior to surgery in an attempt to prevent the follicles from maturing and reaching their chemotherapy-sensitive stage. Patient number 4 underwent a laparoscopy to assess the possibility of cryopreservation of ovarian tissue which was disregarded due to the presence of "jelly belly" around both adnexa. The patient refused preoperative oocyte retrieval for in vitro fecundation. At the time of CRS, both adnexa could be conserved. No patient received postoperative systemic chemotherapy.

Two pregnancies were reported after the diagnosis of PMP and before CRS and HIPEC, with the support of the medical team. Close monitoring with sonography and magnetic resonance imaging was performed in order to enable a premature delivery in case of progress of the underlying disease. Both women delivered healthy newborns (in one case twins) and then undergone CRS and HIPEC. In one case (the women who delivered twins) the pregnancy was obtained thorough *in vitro* fecundation as she had a problem of infertility (a laparoscopy for infertility had permitted the diagnosis of PMP), while the other woman conceived spontaneously.

One case was reported of childbearing via a surrogate mother in a woman who had undergone eggs harvesting 2 months prior to CRS and HIPEC for PMP. Her husband was the father of the embryos. The eggs were maintained for 4 years before implantation into a surrogate mother, which delivered healthy twins.

**DISCUSSION**

The effects of HIPEC in terms of fertility (due to postoperative adhesions or ovarian toxicity) are unknown, but it makes sense to think they are adverse. Very few pregnancies have been reported after fertility-conserving surgery with associated intraperitoneal chemotherapy without hyperthermia [10-13]. These reports support fertility-conserving surgery when possible, even in patients with advanced disease. Only one pregnancy after CRS and HIPEC has been reported to date [14]. It was a spontaneous pregnancy as it was also the case in the seven patients reported here.

This survey was not conducted systematically to assess fertility; its main objective was to discover any pregnancies. We can not estimate the true rate of conceiving as we know neither the exact number of pregnancies (risk of pregnancy not reported to the surgical team), nor the total number of previously fertile women having undergone CRS and HIPEC in the participating centres. Despite asking the surgical teams for their knowledge of patients undergoing medical assistance for childbearing after CRS and HIPEC, this was probably underreported as surgeons are not directly involved in such a proceeding (although sometimes consulted). A bias of declaration may exist in this setting, carrying on an optimistic message about fertility.

However, eight spontaneous pregnancies after CRS and HIPEC are a good reason to think that the effect of surgery, heat and chemotherapy on the adnexa and uterus is limited in terms of fertility. Pregnancies have occurred as soon as 14 months after the procedure and most of them within the following 3 years. Birth control seems warranted in women in childbearing age if their reproductive organs were spared during the cytoreductive surgery.

The question of timing of a pregnancy after HIPEC in an interesting one. Delaying pregnancy some years could achieve a longer disease-free period and a lower risk of relapse and teratogenic effects of chemotherapy; but it carries an increased risk of age-related

infertility. Moreover, the recurrences after PMP do not usually appear in the first year after surgery and, even if it was the case, pregnancies may be safe in the presence of these diseases, as shown in this and other reports [15, 16]. It is not the same with mesothelioma, in which the recurrences are usually earlier. The teratogenic effects of chemotherapy on germ cells are well-known. They may cause infertility, miscarriages or congenital malformations. The present survey was not designed to assess fertility and no miscarriage after HIPEC has been reported, although this report could not capture such information. All newborns except one were healthy. We do not know if the congenital diaphragmatic hernia appearing in the child of patient 4 was a result of her previous treatment. A period of two years between HIPEC and childbearing could be a good compromise between disease-related and childbearing-related aspects, although a case by case approach is warranted.

After intravenous chemotherapy, an increased risk of premature ovarian failure has been reported. This is more likely to occur in older women [17]. In the present series, 5 out of 7 women were under 30 years of age at the time of CRS and HIPEC (and all of them under 35). It is possible that older reproductive-aged women may have more difficulties to conceive or can required assisted medical reproduction techniques. The use of a GnRH analogue prior to and during chemotherapy (as it was the case in patient 2) has been suggested in order to preserve gonadal function [18].

Urgent *in vitro* fertilization is a promising approach for preserving fertility in cancer patients prior to chemotherapy. Current treatment protocols offer a minimal time delay until the treatment is started. The ovarian stimulation outcomes are comparable to those of women with infertility from other causes [19]. As hysterectomy and ovariectomy are often required during CRS, this possibility should be offered to all women in childbearing age before undergoing radical surgery for peritoneal neoplasms. Further, retrieving oocytes through a

cancer filled peritoneal cavity imparts its own risk of dissemination or port site seeding, which may limit the utility of this approach [20].

All pregnancies occurred in women with PMP or mesothelioma. These diseases appear more frequently in younger people and ovarian conservation is more easily achieved than in peritoneal carcinomatosis from colorectal or ovarian origin. Pseudomyxoma peritonei syndrome is not rare among women attempting pregnancy and evaluated for infertility [21]. That was the case of patient 4, in which the diagnosis of pseudomyxoma was established during the workup for infertility. A few cases have been reported of pseudomyxoma peritonei diagnosed during pregnancy, most of the times with a good outcome. In this situation it has been emphasized the importance of avoiding caesarean section, as the abdominal incision will allow for mucinous cancer cells to implant and progress within the abdominal wall and parametrial tissues, thus compromising the completeness of CRS and the likelihood of a curative result [22]. All patients were treated with mitomycin C and/or cisplatin, which are the drugs preferred for those diseases. The effects of other drugs used for peritoneal carcinomatosis from colorectal, gastric or ovarian origin remain unknown.

We can conclude that childbearing after cytoreductive surgery and heated intraperitoneal chemotherapy is possible. The question of fertility should be raised and discussed in women in reproductive age, prior to surgery. Fertility preserving or protecting procedures (preoperative treatment with GnRH analogues, oocyte retrieval with in vitro fertilization and embryo cryopreservation, cryopreservation of ovarian tissue) could be performed. When the genital organs are conserved, women may be able to conceive spontaneously. Multidisciplinary decision making involving surgical oncologists and fertility specialists is important.

**ACKNOWLEDGMENTS**

This work was supported by a grant from the University Hospital of Dijon and the Regional Council of Burgundy 2009. The authors thank Peggy Jourdan-Enfer (Clinic Research Unit, Lyon) for collecting data and mailing the questionnaires and Agnès Maurer (Clinic Research Unit, Dijon) for her help with administrative formalities and CNIL and CCTIRS submission. Pablo Ortega-Deballon had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**REFERENCES**


1. Verwaal VJ, Bruin S, Boot H et al. 8-Year follow-up of randomized trial: cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy in patients with peritoneal carcinomatosis of colorectal cancer. Ann Surg Oncol 2009; 15: 2426-32.
2. Elias D, Lefevre JH, Chevalier J et al. Complete cytoreductive surgery plus intraperitoneal chemohyperthermia with oxaliplatin for peritoneal carcinomatosis of colorectal origin. J Clin Oncol 2009; 27: 681-5.
3. Elias D, Gilly FN, Quenet et al. Pseudomyxoma peritonei: a french multicentric study of 301 patients treated with cytoreductive surgery and intraperitoneal chemotherapy. Eur J Surg Oncol 2010; 36: 456-62.
4. Yan TD, Deraco M, Baratti D et al. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for malignant peritoneal mesothelioma: multi-institutional experience. J Clin Oncol 2009; 27: 6237-42.
5. Glehen O, Mohamed F, Gilly FN. Peritoneal carcinomatosis from digestive tract cancer: new management by cytoreductive surgery and intraperitoneal chemohyperthermia. Lancet Oncol 2004; 5: 219-28.
6. Sugarbaker PH. Building on a consensus. J Surg Oncol 2008; 98: 215-6.
7. Esquivel J. Technology of hyperthermic intraperitoneal chemotherapy in the United States, Europe, China, Japan, and Korea. Cancer J 2009; 15: 249-54.
8. Portilla AG, Sugarbaker PH, Chang D. Second-look surgery after cytoreduction and intraperitoneal chemotherapy for peritoneal carcinomatosis from colorectal cancer: analysis of prognostic features. World J Surg 1999; 23: 23-9.

9. González-Moreno S, Kusamura S, Baratti D, Deraco M. Postoperative residual disease evaluation in the locoregional treatment of peritoneal surface malignancy. J Surg Oncol 2008; 98: 237-41.
10. Ward BH, Harvey VJ. Pregnancy after treatment of endodermal sinus tumor: case report with five-year survival. Br J Obstet Gynaecol 1982; 89: 769– 70.
11. Shaves M, Kamps RR, Laufman LR, Rumowicz CD. A successful term pregnancy following the systemic and intraperitoneal administration of cisplatin chemotherapy. Gynecol Oncol 1990; 39:378–80.
12. Niwa K, Morishita S, Murase T et al. Successful pregnancy in a patient with pseudomyxoma peritonei arising from ovarian mucinous cystadenocarcinoma treated with cisplatin. Gynecol Oncol 1995; 59: 398-400.
13. Smaldone GM, Richard SD, Krivak TC et al. Pregnancy after tumor debulking and intraperitoneal cisplatin for appendiceal carcinoid tumor. Obstet Gynecol 2007; 110: 477-9.
14. Kyser K, Bidus MA, Rodriguez M et al. Spontaneous pregnancy following cytoreduction with peritonectomy and hyperthermic intraperitoneal chemotherapy. Gynecol Oncol 2006; 100: 198-200.
15. Pekin T, Coşar E, Dedeoglu N et al. Diffuse malignant epithelial peritoneal mesothelioma in pregnancy. A case report and literature review. Eur J Gynaecol Oncol 2004; 25: 119-22.
16. van Bijsterveldt C, Willemsen W, Bulten J. Peritoneal benign mesothelioma during and after two pregnancies. Eur J Obstet Gynecol Reprod Biol 2006; 127: 265-6.
17. Revel A, Laufer N. Protecting female fertility from cancer therapy. Mol Cell Endocrinol 2002; 187: 83-91.

18. Blumenfeld Z, Eckman A. Preservation of fertility and ovarian function and minimization of chemotherapy-induced gonadotoxicity in young women by GnRH-a. J Natl Cancer Inst Monogr 2005; 34: 40 – 5.
19. Michaan N, Ben-David G, Ben-Yosef D et al. Ovarian stimulation and emergency in vitro fertilization for fertility preservation in cancer patients. Eur J Obstet Gynecol Reprod Biol 2010; 149: 175-7.
20. Lee SJ, Schover LR, Partridge AH et al. American Society of Clinical Oncology recommendations on fertility preservation in cancer patients. J Clin Oncol 2006; 24: 2917-31.
21. Narvekar S, Vijaykumar P, Shetty N et al. Successful pregnancy in a patient with pseudomyxoma peritonei following in-vitro fertilization using donor eggs. J Hum Reprod Sci 2008; 1: 90-2.
22. Haase E, Yoo D, Sugarbaker PH. Management of appendiceal pseudomyxoma peritonei diagnosed during pregnancy. World J Surg Oncol 2009; 7: 48.