

Carcinogenic uterine risk of repeated abortions: hormone receptors tumoral expression

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Abstract

The main objective of this study is to draw the attention that repeated induced abortions in the women's physiological history are very dangerous and could lead to developing uterine cancer. The legislation regarding this practice is variable in different countries. Relevant information in the field concerning the numerous risk factors that appear with abortions must be taught in schools before girls start their sexual life and can help avoiding the complications that may follow. Also, the abortion should be an extreme measure that must be used only in extreme cases that threaten the mother's life or imply the health of the future child. The study comprised 258 women diagnosed with endometrial carcinoma, without any risks factors for this type of cancer, which were questioned regarding the abortions in previous history. The results show that the age when the uterine carcinoma appears is even lower as the number of abortions is higher and the number of this type of cancer cases is directly proportional with the number of abortions suffered. In order to avoid this fact we have to pay more attention to the legislation and education of the patients. Also, we followed the expression of both estrogen and progesterone hormone receptors, in the case of uterine cancer that occurred in women who had abortions in history compared to the expression of hormone receptors in the case of patients who did not have abortions.

Keywords: induced abortion, carcinogenic risk, uterine carcinoma, hormone receptors.

Introduction

In the last years, the incidence of the endometrial carcinoma is growing continuously all over the world, and it tends to dominate the oncological pathology of the female genital apparatus, becoming the most frequent form of cancer among women in the developed countries [1–4].

This type of cancer affects especially the post-menopausal women and registers a regular increase and significant incidence in the developed countries. Because of its early symptoms, most of the times, it is diagnosed in early stages and this is the reason why the rate of mortality has increased insignificantly compared to its incidence [2–5].

There are two major types of uterine cancer – type 1 and type 2 –, different biologically, clinically, and pathologically [6–8]. The most frequent is type 1, with its development determined by the increase in the level of estrogens, insufficiently contra-balanced by the progesterone. While the type 1 lesions are hormonally sensible and represent more than 80% of the endometrial cancer, the ones of type 2 are less hormonally sensible, appear more frequently in older women, growing in an atrophic medium and are usually detected in an advanced stage [6–8]. Other forms of endometrial cancers are classified as subtypes and are rarer. Also, many subtypes may be a combination of mixed adenocarcinoma, which appear in less than 10% of the cases.

The abortion, regardless of the type – therapeutic, induced or spontaneous –, is accompanied by serious health consequences, manifested through immediate complications or through complications which develop over time.

The legislation regarding this practice is variable in different countries: some countries are for a complete interdiction, and some for the free will of a person.

The results of previous studies indicate an association of menstrual and reproductive factors, with endometrial cancer [9]. Some factors, such as early menarche, late menopause, infertility and null parity, are positively correlated with the risk of endometrial cancer, while high parity, late menarche, early menopause, history of using oral contraceptive pills, and short period after the last delivery at term are considered protective factors [5]. The studies on induced abortions or other types of abortion concerning this type of cancer are not fully coherent; some studies observe a positive correlation [10], others negative correlation [11, 12], and others observe no type of relation between abortion and endometrial cancer [13].

The main objective of this study is to determine the characteristics of the woman with endometrial cancer, which had in her history repeated abortions, and the correlation between these characteristics and the number of abortions.

Within our study, we followed also the expression of estrogen and progesterone hormone receptors (ER and PR),

in the case of uterine cancer that occurred in women who had abortions in history, compared to the expression of hormone receptors in the case of patients who did not have abortions.

☞ Patients, Materials and Methods

Two hundred and fifty-eight women aged between 25–50 years, with endometrial cancer, were included in the study. Patients who had repeated abortions in the physiological history were included, and the women who presented risks factors [obesity – body mass index (BMI) >30 kg/m², family history of uterine cancer, diabetes mellitus, null parity, estrogen therapy without progesterone] were excluded.

The ultrasound evaluation was performed by abdominal ultrasound technique using the abdominal ultrasound apparatus Toshiba.

The samples for performing the histopathological (HP) examination were obtained from surgical samples after total hysterectomy, and coloration with Hematoxylin–Eosin (HE) staining was performed. The medical history of these patients was evaluated, including the following variables: age, menopausal status, numbers of sexual partners, age when they began their sexual life, and the number of abortions.

There were analyzed 50 cases of endometrial carcinomas, of which 27 came from patients who presented abortions in the case history, and the rest of the cases ($n=23$) have constituted the control group.

Two independent pathologists evaluated the cases. The cases were quantified by the “hot-spot” method, including three tumor areas with the highest hormone receptor expression at HPF (high power field).

Paraffin-embedded blocks were sectioned at 4 µm, HE stained and incubated with rabbit monoclonal antibodies ER (clone SP1) and PR rabbit monoclonal antibody (clone 1E2). The immunohistochemistry technique was performed by the automatic method (BenchMark GX), in accordance with the instructions of Ventana Medical Systems, Inc., Tucson, AZ, USA.

Quality control was performed through a slide in which the primary antibody was omitted. This was considered as being the negative control. The positive control was performed using a luminal A-type of invasive breast carcinoma.

☞ Results

The average age was 43 and only 5% of the women were in postmenopausal status (Table 1). The patients have in their history at least one abortion, the majority (79.1%) have induced abortions in the first three months of pregnancy, the rest presented spontaneous abortions (Table 2). More than 50% of the patients (53.5%) are from the category of patients who had a higher number of induced abortions, and only 8.5% of the category with a lower number of abortions. This shows that the carcinogenic risk for uterus carcinoma is directly proportional with the increase in the number of repeated induced abortions.

Table 1 – Characteristics of the studied group

Characteristics		No.	%
Provenience area	Urban	92	30.2
	Rural	213	69.8
Profession	Housewives	207	67.9
	Intellectuals	98	32.1
Age groups [years]	26–30	43	16.7
	31–40	162	62.8
	41–50	53	20.5
Menopausal status	Pre-menopausal	245	95
	Peri-menopausal	0	0
	Post-menopausal	13	5

Table 2 – Characteristics of the abortions

Characteristics		No.	%
No. of abortions	1–4	22	8.5
	5–9	98	38
	10–16	138	53.5
Place of abortion	Empiric	48	18.6
	Hospital	210	81.4
Type of abortion	Spontaneous	54	20.9
	Induced	204	79.1
Month of pregnancy	II	181	70.2
	III	77	29.8
Complications during abortions	Bleeding	145	56.2
	Infections	62	24
	Sepsis	51	19.8

All of them suffered immediate complications, after the abortions were performed; the most frequent complication was bleeding (56.2%), followed by infections (62%), and sepsis (19.8%).

The examination with the abdominal ultrasound brought up the suspicion of the diagnosis of uterine carcinoma. The HP examination of all the studied cases confirmed the diagnosis of uterine cancer, and the different HP types of endometrial adenocarcinoma are presented in Table 3. It is important to note that the appearance of the uterus is very inhomogeneous and enlarged at the abdominal ultrasound examination as shown for the first case presented in Table 3. This 32 years old patient, with 16 induced abortions in the physiological history, presented one year ago an episode of menstrual bleedings with two weeks duration, clots and pain, but this stopped spontaneously and therefore the patient did not visit a physician. Also, in Table 3 are shown the abdominal ultrasound images of other cases of uterine carcinoma in correlation with the number of induced abortions and age of the patients.

The age when the uterine carcinoma appears is even lower as the number of abortions is higher. The average age of the patients with 10–16 abortions was 34 years, eight years lower in comparison with the patients with 5–9 abortions and 14 years lower in comparison with the women with 1–4 abortions, as it is shown in Table 4.

These women started their sexual life very early; most of them had more than six sexual partners (70%) and had an initial abortion (Table 5).

Regarding paraclinical tests, which can indicate the presence of an oncological uterine pathology, only 2% of the patients had the test for the human papilloma

virus (HPV) positive, 98% had the HPV test negative, 85% and 88%, respectively had Babeş–Papanicolau (BP)

test positive and positive tumor markers, according to Table 6.

Table 3 – Some studied cases of uterine carcinoma


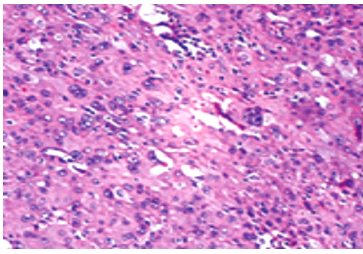
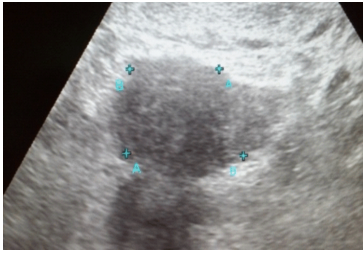
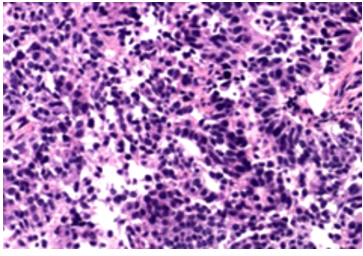

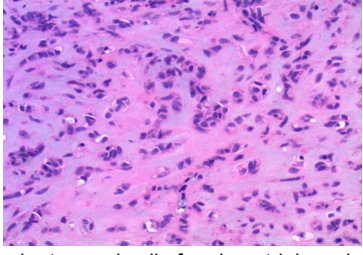
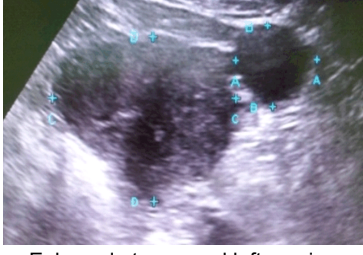
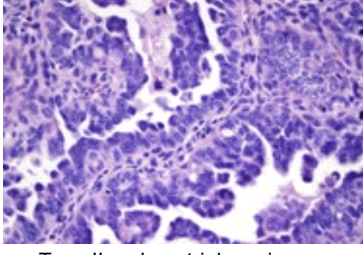
Case No.	Abdominal ultrasound – uterine carcinoma	Histopathology examination (Hematoxylin and Eosin staining)
1. Young woman, 32 years old, with 16 abortions in the past	 Very enlarged uterus, very inhomogeneous, hyperechogenic.	 Giant cell carcinoma of the endometrium (HE staining, ×40).
2. Young woman, 29 years old, with eight abortions in the past	 Enlarged uterus with middle strangulation, inhomogeneous.	 Papillary endometrial carcinoma (HE staining, ×100).
3. Young woman, 35 years old, with 10 abortions in the past	 Normal dimensions uterus, hyperechogenic and with fine line inhomogeneous inside.	 Granular tumoral cell of endometrial carcinoma (HE staining, ×100).
4. Young women, 33 years old, with 12 abortions in the past	 Enlarged uterus, and left ovarian cyst.	 Type II endometrial carcinoma (HE staining, ×100).

Table 4 – The age regarding the number of abortions

No. of abortions	No. of cases	Mean age [years]
1–4	22	48 (46–50)
5–9	98	42 (28–48)
10–16	138	34 (25–38)

Table 5 – The age of onset sexual life and the number of sexual partners

Factors		%
Age of onset of sexual life [years]	<15	87
	>15	13
No. of sexual partners	>6	70
	<6	30
Initial abortion	Yes	92
	No	8

Table 6 – HPV, Babeş–Papanicolau test and tumor markers

Factors		%
Infection with the human papilloma virus (HPV)	Yes	2
	No	98
Babeş–Papanicolau (BP) test	+	85
	–	15
	+	88
Tumor markers	–	12

The analysis of our study reveals a small percentage difference (5.4%) between the expressions of estrogen hormone receptors in the case of abortion-associated carcinoma, compared to the group of patients in which the endometrial carcinoma is not associated with abortion.

From the perspective of the expression of progesterone hormone receptors, it is noted a much higher percentage difference (10.4%) between the two studied groups (Table 7).

What can be remarked when we analyze the obtained data in absolute value is the distribution of the expression of estrogen hormone receptors in the two studied groups. The minimum–maximum variation is higher in the group of patients associated with abortion ($n=384$), compared to the reference group, where differences are lower ($n=211$).

The same analysis applied to progesterone hormone receptors reveals the fact that the difference is higher in

the abortion associated group ($n=446$), compared to the group of patients, in which endometrial carcinoma is not associated with abortion ($n=223$) (Figures 1–4).

Table 7 – Expression of estrogen and progesterone hormone receptors

ER / PR expression	Carcinoma associated with abortion	Carcinoma not associated with abortion
ER %	59.6	54.2
ER score – medium/min./max.	596/389/773	542/476/687
PR %	58.7	69.1
PR score – medium/min./max.	587/286/732	691/543/766

ER: Estrogen receptor; PR: Progesterone receptor.

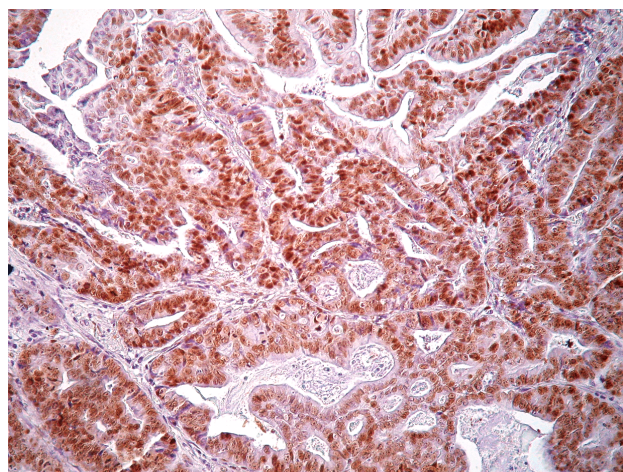


Figure 1 – Endometrial carcinoma: high expression of PR in carcinoma not associated with abortion (Anti-PR antibody immunomarking, $\times 40$). PR: Progesterone receptor.

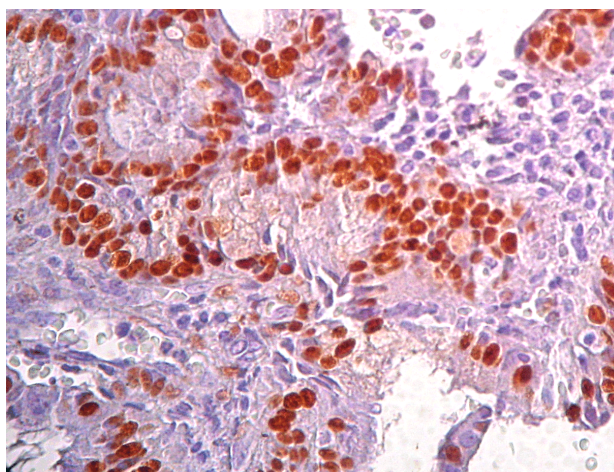


Figure 2 – Endometrial carcinoma: detail of PR high expression in carcinoma not associated with abortion, homogeneous and of high intensity (Anti-PR antibody immunomarking, $\times 100$). PR: Progesterone receptor.

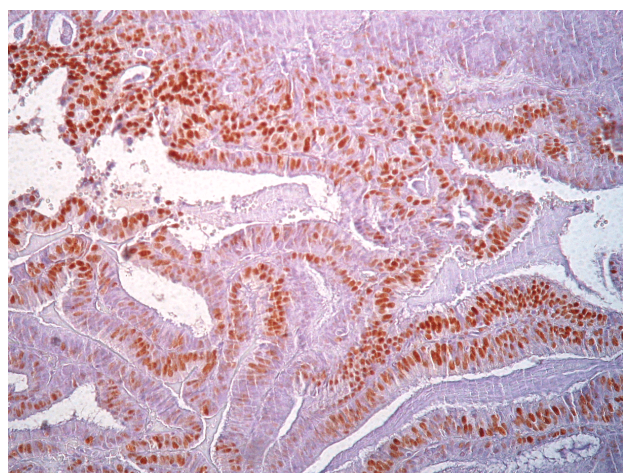


Figure 3 – Endometrial carcinoma: decreased expression of PR in carcinoma associated with abortion (Anti-PR antibody immunomarking, $\times 40$). PR: Progesterone receptor.

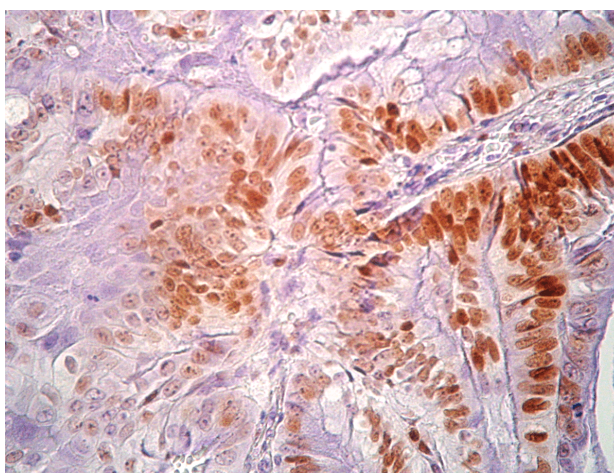


Figure 4 – Endometrial carcinoma: detail of PR expression in carcinoma associated with abortion, inhomogeneous and of variable intensity (Anti-PR antibody immunomarking, $\times 200$). PR: Progesterone receptor.

Discussion

In this study, we observed an association between the increased number of abortions and the increased incidence of endometrial cancer, with a young age at the apparition of the disease.

The endometrial cancer, that is the most frequent uterine cancer, was present in more than 95% of the cases [5], and in women who live in developing countries, it is

the most frequently found form of cancer. Increase incidence of this pathology especially in developed countries is attributed to the lifestyle changes and to the hope of having a better life [14, 15].

This type of cancer appears more frequently in the women at menopause, older than 50 years, with average age of onset at 63 years [2, 5, 14, 16, 17].

In this study, all the women had been diagnosed with endometrial cancer before the age of 50, at a significant

difference compared to the average age with the maximum prevalence indicated in other studies and had an increased number of abortions.

A very high percentage of uterine carcinoma cases in young women between 32–34 years or less than that between 25–29 years is noticeable after this extremely dangerous practice. From the physiological antecedents of these young patients are very important the high number of induced abortions at young age, in correlation with the abdominal ultrasound image of the uterus, according to images described in Table 3.

An important remark is that the tumor marker for the uterine carcinoma was not increased in all cases; in some cases, the values were normal. Therefore, it did not draw attention on the diagnosis and was a nonspecific marker.

The HP examination confirmed the presence of uterine cancer. Similarly to the cases of other tumors, the HP examination has a special importance in determining the type of cancer [18–20].

If we compare the results obtained within our study, in the group of patients with uterine carcinoma without a medical history of abortion, we notice that they are consistent with those in the specialty literature. In the study of Srijaipracharoen *et al.*, the results are 59.3% for ER and 65.7% for PR, respectively. We should mention that the expression of hormone receptors in our case is slightly higher compared to the data presented [21].

In the case of endometrial carcinoma, one of the hypotheses, which would explain the association with the medical history of abortion, is the so-called “non-balancing estrogen secretion” theory. It is considered that excess estrogen secretion is a risk factor in the development of endometrial carcinoma. The observation started from the patients with spontaneous abortion at an advanced age, not followed by a new full term pregnancy [10].

By analogy, many studies attempted to achieve a parallel between the caused abortions, regardless of age, and the loss of pregnancy at advanced ages. In these cases, it is noticed an increased level of estrogen compared to the progesterone value. In fact, this increased value is obtained by the decreasing value of progesterone. The higher the number of abortions, the more we consider the hormonal imbalance tends to be higher. Data obtained within our study (not shown in the article) reveal a decrease in the PR expressiveness in patients with an increased number of abortions.

In recent years, numerous studies have been carried out in which it has been analyzed the corroboration of abortion with different types of cancers: ovarian, cervical, including colorectal. In most studies, the type of abortion is not specified (spontaneously or provoked).

The comparative analysis of our data obtained in the two groups reveals that ER expression is slightly increased in patients with a history of one or more abortions. The comparative analysis of the minimum and maximum values reveals a low variability between the two studied groups.

What seem to be significant are the data obtained in the comparative analysis of the PR expression. Patients with a history of abortion have a much lower expression

compared to patients from the reference group (58.7% vs. 69.1%).

If we evaluate the result of the minimum–maximum differences between ER and PR in the two studied groups, the difference is statistically lower in the estrogen receptor group (173 vs. 223).

The variability between the two groups reported in percentages is 22.42%

This contraceptive method should be avoided as much as possible, and substituted with other modern contraceptive methods [22, 23]. Young women should know about the risks of uterine carcinoma apparition after repeated induced abortions, because this is a mechanical trauma of the uterine mucosa and the uterine muscles, which develops morphological disturbances of the cells at this level. After the mechanical trauma, a scar in the conjunctive tissue appears at the respective level, but, more than that, some cells start malignant changes and begin to develop a uterine carcinoma.

The abortion should be considered as a final measure that can be taken, and it should be used only in extreme cases when the pregnancy state threatens the mother’s life or implies the health of the future child.

How many abortions could be performed during the women’s life without taking any risks for their health? The reality and ideal is none. Starting from this point of view, the women have to pay attention to the prophylaxis.

We consider that as soon as the women will understand the negative consequences of this dangerous practice, they will be very careful in the future with their health.

✎ Conclusions

The most important conclusion of this study, at the same time with some clinical cases presented, is that repeated induced abortions in the past represent a carcinogenic risk for a carcinoma of the uterus, and the women must be very well informed about this dangerous practice since early ages, in school or family education, before starting the sexual activity. Also, a very early age of starting the sexual life is a risk factor, often because at a younger period in life, the women may not have enough material possibility and knowledge to raise in good conditions and environment a child. A large number of cases have an abortion performed, and this could be the beginning for many others. Our results show that the carcinogenic risk for uterus carcinoma is directly proportional to the increased number of the repeated induced abortions and inverse proportional with the age. As a general conclusion, we can say that the importance of all data and cases presented in this paper is that it stimulates a more accentuated attention for legislation in countries that allow abortion on demand. In the same time, it obliges the specialists to focus on the choice to perform an abortion or not, namely the implementation and enhancement of a healthy education early and continuously for girls/women, to prevent and even stop the abortions.

Conflict of interests

The authors declare that they have no conflict of interests.

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