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Simultaneous Nephron-Sparing Surgery and Caesarian Section for the Treatment of Renal Cell Carcinoma in Pregnancy: Case Report and Review of the Literature

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1. Introduction

Renal cell carcinoma (RCC) accounts for about 3% of all adult malignancies and is the most lethal urological cancer. Although extremely rare in pregnant women, it is the commonest urological neoplasm in pregnancy occurring in 1 in 1000 cases (Walker, JL., & Knight, EL., 1986). It is potentially curable with prompt diagnosis and correct management. However, treatment of the disease is a substantial challenge for both, urologist and obstetrician.

Over 70 cases of RCC in pregnancy have been reported in literature. 95% of them are clear cell type, with a poorer prognosis than the rest 5% that are chromophobe type. Women with these tumors may present at any stage of the pregnancy. Only 26% of them describe the classical triad of: loin pain, palpable mass and haematuria. The most common mode of presentation of the disease is a palpable mass (88%) and pain (50%). Haematuria implies collecting system invasion and occurs in 50% of the cases. However, haematuria in pregnant women is faint due to other possible causes, including: urinary tract infection, calculi and hydronephrosis (Pearson, GAH., & Eckford, SD., 2009). Other rare forms of presentations are: hypertension, haemolytic anaemia and hypercalcaemia (Monga, et al., 1995; Usta, IM., et al., 1998). With the advent of ultrasound there has been a change in presentation of the disease with diagnosis more frequently made incidentally during ultrasound examination performed for other reasons (Fynn, J., & Venyo, AKG., 2004).

Diagnostic evaluation of a pregnant woman with renal mass requires special consideration combining non-invasive techniques with as little radiation exposure as possible to the mother and fetus. As a first step, urine has to be sent for cytology. Abdominal CT and intravenous pyelography (IVP) are frequently used in the evaluation of non-pregnant patients and should be avoided due to the unsafe radiation exposure to fetus. Renal radionuclide scans being used to determine function of a contralateral kidney has to be replaced by Doppler scan. Ultrasonography (US) is the safest method for diagnosis of the renal mass in pregnant woman with the similar to IVP and CT sensitivity of 85% (Warshauer, DM., et al., 1988). Magnetic resonance imaging (MRI) is also suitable, due to the least radiation exposure and no harm to pregnant woman. However, it should be stressed

that chest CT remains the most sensitive method for diagnosis of pulmonary metastases. The US and MRI are the investigations of choice adequately identifying, differentiating and staging the solid renal masses in pregnancy.

The management of RCC in pregnant woman should depend on tumor biology and age of gestation. Decision to operate and prevent further tumor spread should be taken in consideration of the degree of fetal maturity. The impact of surgical and adjuvant therapy on the potential for future pregnancies should be also considered.

The most frequent form of treatment of RCC in pregnancy is open or laparoscopic radical nephrectomy (RN) followed-up by spontaneous delivery (Pearson, GA., & Eckford, SD., 2009; Gnessin, E., et al., 2002; Qureshi, F., et al., 2002; Monga, M., et al., 1995; O'Connor, JP., et al., 2004; Lee, D., & Abraham, N., 2008). RN with or without termination of pregnancy (Loughlin, KR., 1995; Usta, IM., et al., 1998; Simon, I., et al., 2008), Caesarean section (CS) followed-up by RN (Stojnić, J., et al., 2009) and simultaneous RN and CS (Kobayashi, T., et al., 2000) have also been reported in the literature. There are no reports on the simultaneous nephron sparing surgery (NSS) and CS in the pregnant women.

Here we report the first case of NSS performed together with CS for the treatment of RCC in the second trimester of pregnancy. The review of the literature discussing the tretment options, timing of the surgery and multidisciplinarity of approach is also given.

2. Case history

A 33 years old female was referred to our center at 24 weeks' gestation without previous history of urological diseases and any subjective complaints. The right renal mass has been found on routine sonography. A 6X6X4.5 cm. solid tumor has been detected on MRI arising from the upper pole of the right kidney (figure 1)**.** Regional lymph nodes were negative. Hepatic and pulmonary metastases have been excluded by abdominal and chest MRI. Renal biopsy has not been performed due to the following reasons: a) the positive predictive value of the imaging findings is so high that a negative biopsy result would not alter the management strategy; b) 10-20% of biopsies are reported to be non-conclusive; c) high risk of complications associated with biopsy (Silverman, SG., et al., 2006).

The tumor was graded according to the Padua anatomical classification and assigned the score 6. According to this score the risk of surgical complications related to the NSS was considered as low. There were no radiological signs of local extension and/or distant metastases. Clinically the tumor was staged as: T1b, N0, M0.

After extensive counseling and consultation with the obstetrician decision has been taken to postpone the operative treatment until the third trimester of gestation as recommended in the literature. The patient was followed-up by: regular urological and obstetrical checkup; sonography once per month; and weekly urinalysis, until maximal chance of fetal viability. The patient was stable without any signs of disease progression until 33rd week of gestation. After re-consulting with obstetric staff, simultaneous NSS and caesarian section was planned at this time point.

Caesarian section has been performed first under epidural anesthesia. A healthy girl weighing 2.4 kg was delivered without any surgical difficulties. The patient was intubated

and operation was continued with open NSS through flank incision. Enucleoresection was performed with arterial clamping and local hypothermia. Cold ischemia time was 15 min. Duration of the NSS was 115 min. Blood loss was less than 100 cc. The renal capsular defect has been covered with free peritoneal graft.

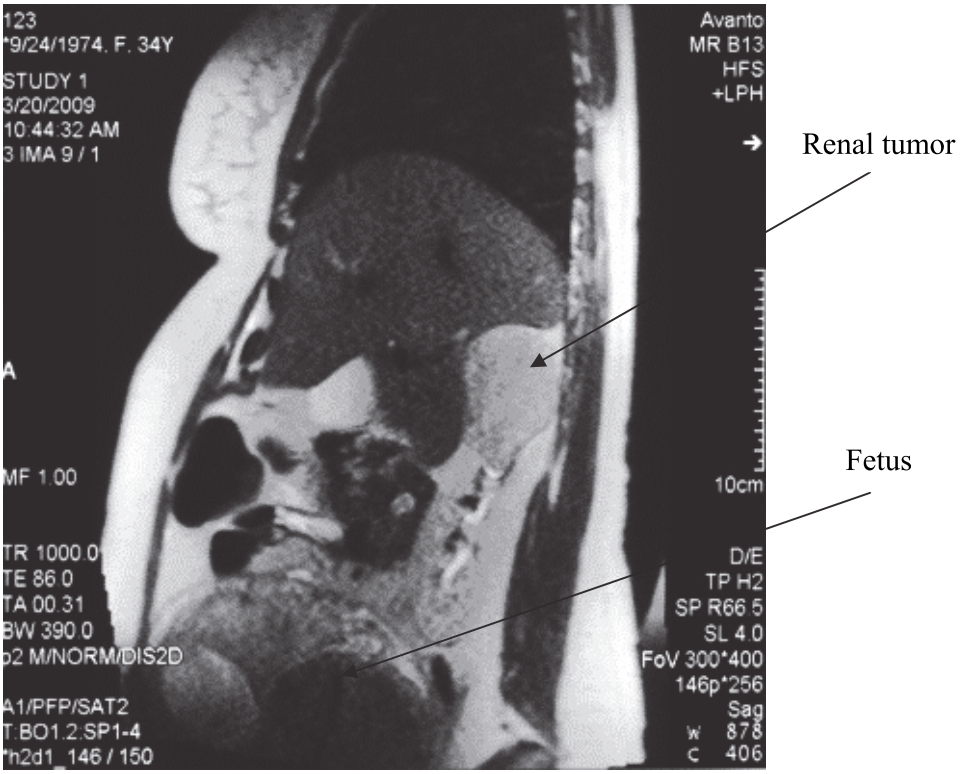

Fig. 1 MRI scan demonstrating right renal mass and the fetus

Postoperative course was uneventful for both, the mother and child. The patient made a good recovery with normal obstetric examinations. Morphology revealed clear cell RCC pT1bN0M0, grade 1. After the follow-up of 30 months the patient is doing well without any signs of the disease recurrence. The child is healthy with normal physical and mental development.

3. Discussion

RN and NSS are the treatments of choice for the patients with RCC. Oncological results and complications of the treatments are extensively evaluated showing excellent outcomes in the patients with local stages of the disease. However, management of RCC in pregnant women is extremely challenging due to the rarity and difficulty of the situation. There are several reports in the literature about the treatment of RCC at different time points of pregnancy. Table 1 describes the cases of the treatment of RCC in pregnancy reported in the literature.

Table 1. Cases of the treatment of RCC in pregnancy reported in the literature

Author	Year of publication	N of cases	Age of gestation at diagnosis	Stage	Treatment	Age of gestation at treatment	Pregnancy outcome
Gladman, MA., et al.	2002	2	14th and 24th weeks	T2N0Mx	RN	17th and 25th weeks	1. Spontaneous delivery at 40th weeks; 2. CS at 40th weeks
Fynn, J., Venyo, AK.	2004	1	12th week	T2N0M0	RN	24th week	CS at 24th weeks
Fazeli-Matin, S., et al.	1998	1	13th week	T2N0M0	NSS	13th week	Spontaneous delivery
Gnessin, E., et al.	2002	2	18th and 16th weeks	T1N0M0 and T2N0M0	RN	18th and 16th weeks	Spontaneous deliveries
Qureshi, F., et al.	2002	1	I trimester	T2N0MX	RN	I trimester	Spontaneous delivery
Lee, D., & Abraham, N.	2008	1	I trimester	-	Lap. nephrectomy	19th week	Spontaneous delivery
O'Connor, J., et al.	2004	1	11th week	T1N0M0	Lap. nephrectomy	19th week	Spontaneous delivery at 38 week
Simon, I., et al.	2008	1	I trimester	-	RN	I trimester	Pregnancy interruption
Pearson, GAH., Eckford, SD.	2009	1	28th week	T2	RN	CS at 34th week	CS at 32nd week
Stojnić, J., et al	2009	1	I trimester	-	RN	II trimester	CS in II trimester
Kobayashi, T., et al.	2000	1	22nd week	T2N0M0	RN	28th week	CS at 28th week

It was believed for a long time that there is no association between RCC and pregnancy. However, more recent studies discovered new facts. Lambe, M., et al. in a Swedish population-based study, found a strong association between the number of births and the risk of RCC. They have shown that the parous women were at a 40% increased risk of RCC compared to nulliparous women (Lambe, M., et al., 2002). It is known that both, normal and malignant renal cells contain oestrogen and progesterone receptors (Ronchi, E., et al., 1984). Chow, WH., et al. have shown an increased risk of RCC in pregnant women with co-existing risk factors like: parity greater than five, obesity, hypertension and diabetes (Chow, WH., et al., 1995). It has been speculated that pregnancy-associated hormonal changes, particularly high oestrogen levels, may act as promoters of malignant change by stimulating renal cell proliferation either directly or via paracrine growth factors (Concolino, G., et al., 1993). Whether these observations have any implications for the biological behavior of malignant renal cells in pregnancy is not clear, but a tendency towards immediate rather than delayed surgery seems to be appropriate. However, as neonatal survival rates increase with increasing gestation at delivery, immediate surgery at early stages of pregnancy is potentially deleterious to fetal health. Therefore, it is extremely important to define whether pregnancy has to be interrupted or allowed to continue if radical nephrectomy is carried out (Fynn, J., & Venyo, AK., 2004).

If the RCC is discovered in the first trimester, immediate surgery is recommended by majority of the authors (Loughlin, KR., 1995; Gladman, MA., et al., 2002). Whether pregnancy should be terminated at this gestation or not is debatable. The decision should be based on the patient's wishes and medical indications. It is important to consider that the risks of miscarriage and teratogenesis are high at this age, making termination a better option for some authors (Fynn, J., & Venyo, AK., 2004). Others however, disagree with this approach (Usta, IM., et al., 1998).

Management of the disease in the second trimester is more challenging. In the late second trimester surgery should be delayed to at least 28 weeks, when the fetal survival of over 90% is achievable (Loughlin, KR., 1995). In the early second trimester however, immediate surgery is recommended by some of the authors due to the low risk of the fetal loss (Fazeli-Matin, S., et al., 1998; Gnessin, E., et al., 2002; Jenkins, TM., et al., 2003).

In the third trimester the fetal lung maturity is established and immediate surgery seems convenient. It has been suggested that CS should not be performed at the time of RN as the kidney is removed through different incision (Walker, JL. & Knight, EL., 1986). If the diagnosis is made in the late third trimester the surgery can be postponed until delivery (Loughlin, KR., 1995).

In case of the metastatic disease the pregnancy should be terminated (Hendry, WF., 1997). There are no reports of patients or fetal metastases so far.

The most frequent form of treatment of RCC in pregnancy is open or laparoscopic RN followed-up by spontaneous delivery. Gladman, MA., et al. reported 2 cases of RCC diagnosed in the second trimester. RN was performed without termination of pregnancy. One patient gave birth to healthy child and the second one underwent emergency CS for fetal distress at forty weeks' of gestation (Gladman, MA., et al., 2002). Two cases of successful open RN in the second trimester have been reported by Gnessin, E., et al., Both patients gave full term spontaneous delivery to healthy children (Gnessin, E., et al., 2002).

Qureshi, F., et al. detected RCC in the first trimester. Immediate RN was performed through a thoraco-abdominal approach. The patient gave birth to a healthy infant at full term by spontaneous vaginal delivery (Qureshi, F., et al., 2002). Lee, D. & Abraham, N., and O'Connor, J., et al., reported the case of RCC discovered in the first trimester. The operation was delayed till the second trimester. Laparoscopic transperitoneal nephrectomy was performed at 19 weeks' gestation in both cases. Both patients delivered a healthy child vaginally at 39 weeks' gestation (Lee, D., & Abraham, N., 2008; O'Connor, J., et al., 2004).

Simon, I., et al. reported a rare case of Von Hippel-Lindau disease in pregnant women presented with haematuria in the first trimester. RN was carried out after pregnancy interruption (Simon, I., et al., 2008).

Pearson, GAH., & Eckford, SD., detected RCC in the third trimester of pregnancy. CS was performed at 32 weeks of gestation followed-up by RN two weeks later. The same approach has been reported by Stojnić, J., et al. (Stojnić, J., et al., 2009).

Simultaneous RN and CS has also been performed for the treatment of RCC detected in the second trimester (Kobayashi, T., et al, 2000). There are no reports on the simultaneous NSS and CS in the literature.

The data on the effect of pregnancy on long-term survival of RCC is very limited. The same is true for the effect of future pregnancies on tumor recurrence. Some authors have reported good clinical results and survival in pregnant women with RCC (Walker, JL. & Knight, EL., 1986). More data on the outcomes of different treatment options, including the effect of subsequent pregnancies on the disease recurrence are needed to answer these questions.

4. Conclusion

The management of a pregnant woman with a malignant solid renal mass should follow certain principles: 1) the welfare of the mother should be main concern, unless she wishes otherwise; 2) management of the patient has to take place in a multidisciplinary setting involving: urologist, neonatologist, obstetrician, radiologist, anaesthetist, and morphologist; 3) the standard surgical treatment of the most stages of RCC is RN or NSS; 4) timing of the surgery depends on biological behavior of the tumor and the neonatal survival rates for the different gestations; 5) In case of widespread metastatic disease, the pregnancy should probably be terminated and the woman has to be treated according to the guidelines recommended for non-pregnant patients. Here we repot the first case of NSS performed simultaneously with CS for the treatment of pregnant woman with RCC. This approach can be considered feasible in women in the second and third trimesters of pregnancy.

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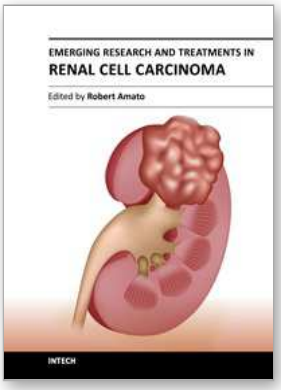

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The field of renal cell cancer has undergone a significant resurgence. This book summarizes up-to-date research and innovative ideas for the future in this rapidly changing field, which encompasses medicine, surgery, radiation oncology, basic science, pathology, radiology, and supportive care. This book is aimed at the clinician or scientist who has an interest in renal cell cancer, whether they are academic or nonacademic. The book covers tumor biology, molecular biology, surgery techniques, radiation therapy, personal testimonies, and present and future treatments of the disease that are on the horizon. The goal was to produce a textbook that would act as an authoritative source for scientists and clinicians and interpret the field for trainees in surgery, medicine, radiation oncology, and pathology.

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