Case Report
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Fertility and reproductive outcomes in woman with adrenocortical carcinoma on mitotane: a case report

Abstract

Adrenocortical carcinoma (ACC) is a rare disease with an incidence of 1 in 1.7 million. Due to its rare occurrence, there is sparse data on fertility or reproductive outcomes for patients with ACC. Our case demonstrates a nulligravida woman with recurrent metastatic ACC on daily mitotane that was diagnosed with an incidental pregnancy. Mitotane crosses the placenta, but the teratogenic effects are unknown. Currently, there are only five case reports published of women with ACC conceived while on mitotane. We present a case of pregnancy in a woman with metastatic ACC who was treated with mitotane.

Keywords: pregnancy, woman, mitotane, adrenocortical carcinoma

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Introduction

Adrenocortical carcinoma (ACC) is an extremely rare disease with an estimated incidence of 1 in 1.7 million.[1] Only 80 to 130 cases are detected each year in the United States.[2] Women are slightly more affected than men. Epidemiologically, these cases tend to arise during the reproductive lifespan with peaks in the first and fifth decades, which poses significant challenges to the patient's fertility options as well as ethical dilemmas. With a 5-year survival rate under 50% for advanced-stage disease (Stage III, IV), these challenges are even more pronounced.[3–5] Herein we present a case of incidental pregnancy in a woman with ACC being treated with mitotane, an adrenolytic agent used as an adjuvant therapy to surgery and radiation. Mitotane is a parent compound of insecticide dichlorodiphenyltrichloroethane (DDT). It is the only approved drug for treatment of advanced ACC. It destroys the adrenal cortex, impairing steroidogenesis.[3–5] Mitotane crosses the placenta, but the teratogenic effects on the developing fetus are unknown. Currently, there are only five published case reports of women with ACC on mitotane who have become pregnant Table 1.[3–7] As a result, there is scant data regarding pregnancy outcomes, neonatal morbidity and safety of mitotane as well as progression of disease; thus, counseling patients poses a significant challenge, especially in the post-Dobbs era. We attempt to provide insight on the medical and ethical dilemmas for patients similar to ours.

Case report

A 30-year-old nulligravida Caucasian female initially presented with new-onset hypertension, episodes of hypokalemia and facial swelling in November 2019, which led to her diagnosis of Cushing syndrome. An evaluation was notable for an elevated morning cortisol level of 33.4 mcg/dL with otherwise unremarkable metanephrines, normetanephrines and aldosterone. CT imaging demonstrated a large right adrenal mass measuring approximately 10 cm. The patient underwent a right adrenalectomy, which revealed a high-grade adrenocortical carcinoma (ACC) histopathological with mitotic count >50/50 HPF.

Treatment continued with adjuvant radiation of 50.4 Gy followed by daily mitotane. However, she never was placed into remission. Six months later, metastatic disease involving her lung, liver, and peri-renal space was identified. Therefore, she underwent locoregional therapy with five rounds of chemotherapy with etoposide, doxorubicin, and cisplatin and additional radiation. Prior to initiating chemotherapy, she was counseled on fertility preservation. Hence, she underwent oocyte retrieval and IVF; she cryopreserved six embryos. Subsequently, repeat imaging demonstrated stable metastatic disease. Complete surgical resection was attempted; a nephrectomy, partial hepatic resection, and partial diaphragmatic resection were performed, but persistent disease remained.

Spontaneous resumption of menstruation began approximately five months after the last cycle of chemotherapy. Meanwhile, she had continued mitotane as long-term monotherapy for ACC. Her menstrual cycles were irregular, occurring every 28 to 40 days and lasting 4 to 5 days. During this time, she had not been using a contraceptive, as she felt her chances of conceiving were minimal based on her history of chemotherapy. Furthermore, due to limited research of the effects of contraceptives on ACC, she was discouraged from all forms of hormone containing contraceptives. Subsequently, she presented for positron emission tomography (PET) scan imaging. Routine testing identified a human chorionic gonadotropin level of 136 IU/L. Her preconception labs were notable for an undetectable DHEA-S and free testosterone, low total testosterone (7 ng/dL), normal thyroid function (TSH 3.3 µIU/mL) and cortisol (1.0 µg/dL), elevated SHBG (411 nmol/L) and ACTH (61 pg/mL), leukopenia (2.7 K/µL) and mitotane level of 13 mcg/mL, confirming iatrogenic adrenal insufficiency. Embryonic cardiac activity was detected by transvaginal ultrasound 11 days after HCG was detected.

Due to the difficulty in assessing a risk-benefit ratio, a multi-disciplinary collaboration involving the oncologist, obstetrician and bioethics division ensued. Since this was a desired, albeit unplanned, pregnancy initially, the oncologist advised her to discontinue the mitotane during pregnancy. As will be discussed below, ACC and mitotane exposure may predispose the fetus to abortion and preterm delivery; however, there are only theoretical risks of dysfunctional adrenal development. In the few neonates exposed to mitotane, no morphological defects or neurologic impairment has been noted. As

for the maternal status, continuing the pregnancy and/or mitotane use was controversial; there is limited discussion in the prior reports as to what guided the mother's decision one way or the other.

Discussion

Mitotane is a parent compound of insecticide dichlorodiphenyltrichloroethane (DDT) and has an extremely long elimination half-life of 18-159 days. Hence, discontinuation of it even at four weeks gestation places an embryo and fetus at risk teratogenicity. It is the only approved medication for treatment of advanced ACC. It works as an adrenolytic agent by destroying the adrenal cortex, thus impairing steroidogenesis.[8] Mitotane has been shown to cross the placenta, but the teratogenic effect on the developing fetal adrenal glands remains unknown.[9]

Five case reports have been published involving utilization of mitotane in pregnancy with known ACC. In case 1, the patient continued using mitotane during pregnancy but experienced a spontaneous abortion of twins at 10 weeks gestation.[4] It is unclear if mitotane was the driving force. In case 2, a mother carried her pregnancy until 31 weeks gestation before requiring a Cesarean section due to HELLP syndrome.[5] Mitotane was continued throughout the pregnancy, and normal child growth and development was noted at the 1-year follow-up.[5] In case 3, mitotane was discontinued at six weeks gestation due to concern for potential teratogenicity. On 16-week ultrasound, she had a morphologically normal female fetus without intrauterine growth restriction and normal appearing adrenal glands. However, an extensive recurrence ensued, and the pregnancy was terminated at 21 weeks gestation due to maternal condition.[3] The patient deceased six months later. In case 4, twenty-one pregnancies in women with adrenocortical carcinoma were summarized, only one pregnancy occurred under mitotane therapy, the pregnancy resulted in an induced termination at 8 weeks.[6] And Case 5, demonstrated uncomplicated term vaginal delivery with no known maternal complications.[7] Further details of each individual case is summarized below Table 1.

Table 1 Summarization of pregnancy for women with ACC on Mitotane

Case, year published	Age	Mitotane use	Fetal outcome	Maternal outcome
1. 2011[4]	28	Serum concentration of 12.5 mg/mL, continued throughout pregnancy	Twin pregnancy, Spontaneous abortion at 10 weeks	No evidence of ACC recurrence at 6 months
2. 2011[5]	28	1g daily, continued throughout pregnancy	Normal neonatal growth and development at 1 year	Premature delivery at 31 weeks via Cesarean section due to HELLP; ACC recurred after delivery
3. 2013[3]	33	Discontinued at 6-week gestation	Pregnancy termination at 21 weeks due to ACC recurrence	Maternal death 6 months after termination
4. 2015[6]	39	Continued throughout pregnancy	Therapeutic abortion at 8 weeks due to maternal request	Liver metastases resolved with resection, survival 8+ years after diagnosis
5. 2018[7]	20	Discontinued at 9-week gestation	APGAR 10/10. Normal growth and neurological development at 3 years old	Vaginal delivery at 40 weeks; No known maternal complications
6.2022 (current)	33	Discontinued at 4-week gestation	Therapeutic abortion at 6 weeks per maternal request	No current known complications

Of the five known cases of pregnancy with mitotane use for patients with ACC, three were terminated prior to viability. Two of the patients had successful deliveries which are described as developmentally normal. Out of the two viable fetuses, one patient had continued mitotane throughout her pregnancy which was complicated by HELLP syndrome, while the other had an uncomplicated pregnancy and delivery. Previous research has demonstrated that mortality rates for ACC are higher amongst pregnant or post-partum women compared to non-pregnant.[10] The survival rate of pregnant women with ACC was found to be 50% at 1 year, 28% at 3 years, 13% at 5 years, and 0% at 8 years.[10] Induced termination during early pregnancy has been described for patients with advances stage ACC due to possible maternal benefits.[11]

The ethical dilemmas that arise in patients with terminal illnesses prove to be complicated. Fertility preservation should be discussed and advised to all patients with any terminal illness. However, a discussion entailing the dilemma of mortality and subsequent childcare is thus inevitable. A multi-disciplinary approach is optimal in the overall management for these patients. In the post-Dobbs era, these dilemmas pose significant repercussions to these patients. For our patient, we discussed the possible pregnancy complications in the setting of ACC (abortion, preterm delivery, HELLP), as well as the unknown effects of mitotane. Because she had cryopreserved embryos already, she desired to continue the mitotane, proceed with an induced termination, with plans of using a gestational surrogate in the future. We would also like to comment on contraceptives for patients with ACC. One study showed possible estrogen receptors that may facilitate tumor development; thus, some oncologists may be reluctant to prescribe estrogen-containing contraceptives.[12] However, pregnancy in patients with ACC obviously pose greater risks than the use of combined contraception. The data reviewed herein does not clearly delineate an effect of pregnancy on ACC; thus, we would argue that any form of contraception is acceptable in these patients.[13]

Acknowledgments

None.

Conflicts of interest

The author declares there is no conflict of interest.

References

1. Coonrod DV, RizkaUah TH. Virilizing adrenal carcinoma in a woman of reproductive age: A case presentation and literature review. *Am J Obstet Gynecol*. 1995;172(6):1912–1914.
2. Wooten MD, King DK. Adrenal cortical carcinoma. Epidemiology and treatment with mitotane and a review of the literature. *Cancer*. 1993;72(11):3145–3155.

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3. Tripto Shkolnik L, Blumenfeld Z, Bronshtein M, et al. Pregnancy in a patient with adrenal carcinoma treated with mitotane: A case report and review of literature. *Journal of Clinical Endocrinology and Metabolism*. 2013;98(2):443–447.
4. Baszko Błaszyk D, Ochmańska K, Waśko R, et al. Pregnancy in a patient with adrenocortical carcinoma during treatment with Mitotane-a case report. *Polish Journal of Endocrinology Tom*. 2011;62(2):186–188.
5. Kojori F, Cronin CMG, Salamon E, et al. Normal adrenal function in an infant following a pregnancy complicated by maternal adrenal cortical carcinoma and mitotane exposure. *Journal of Pediatric Endocrinology and Metabolism*. 2011;24(3–4):203–204.
6. De Corbière P, Katrin Ritzel, Laure Cazabat, et al. Pregnancy in women previously treated for an adrenocortical Carcinoma. *Journal of Clinical Endocrinology and Metabolism.* 2015;100(12):4604–4611.
7. Magkou D, Cao CD, Bouvattier C, et al. Foetal exposure to mitotane/Op'DDD: Post-natal study of four children. *Clin Endocrinol (Oxf).* 2018;89(6):805–812.
8. Lo Iacono M, Soraya Puglisi, Paola Perotti, et al. Molecular mechanisms of mitotane action in adrenocortical cancer based on in vitro studies. *Cancers*. 2021;13(21):5255.
9. Leiba S, Weinstein R, Shindel B, et al. The protracted effect of o,p'-DDD in Cushing's disease and its impact on adrenal morphogenesis of young human embryo. *Ann Endocrinol (Paris).* 1989;50(1):49–53.
10. Abiven Lepage G, Joël Coste, Frédérique Tissier, et al. Adrenocortical carcinoma and pregnancy: Clinical and biological features and prognosis. *Eur J Endocrinol*. 2010;163(5):793–800.
11. Lamb M, Farley D. Adrenal Tumors and Pregnancy. *In Adrenal Glands*. 2005;5:103–116.
12. Sirianni R, Fabiana Zolea, Adele Chimento, et al. Targeting estrogen receptor-α reduces adrenocortical cancer (ACC) cell growth in vitro and in vivo: Potential therapeutic role of selective estrogen receptor modulators (SERMs) for ACC treatment. *Journal of Clinical Endocrinology and Metabolism*. 2012;97(12):2238–2250.
13. Fassnacht M, Olaf Dekkers, Tobias Else, et al. European society of endocrinology clinical practice guidelines on the management of adrenocortical carcinoma in adults, in collaboration with the European Network for the study of adrenal tumors. *European Journal of Endocrinology*. 2018;179(4):1–46.

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