

## Letter to the Editor

## MULTIPLE ENDOCRINE NEOPLASIA 2A AND PREGNANCY: A MEDICAL AND ETHICAL CHALLENGE

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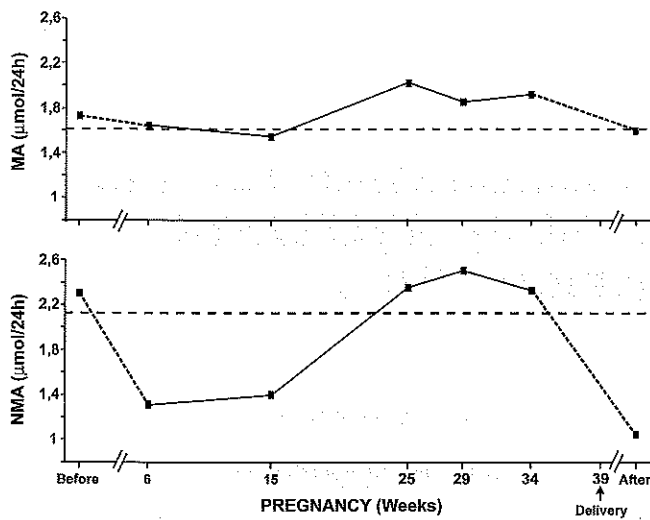
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Sir,

Multiple Endocrine Neoplasia 2A (MEN 2A) is an autosomal dominant syndrome characterized by an activating mutation of the RET proto-oncogene (1, 2). Diagnosis of MEN 2A implies a genetic analysis of the patient and his or her relatives as well as a periodic lifelong supervision of the potential manifestations of the syndrome. These include medullary thyroid carcinoma (MTC) in 90% of cases, pheochromocytoma in 50% and hyperparathyroidism in 20-30% (1, 2). The follow-up and management of these endocrinopathies must be guided by a risk stratification according to the specific RET codon mutations (1). Whereas MTC is the most aggressive, thus requiring early thyroidectomy, during childhood if possible, pheochromocytoma raises great concern because of its life-threatening manifestations. When a woman with MEN 2A mutation is of childbearing age or is pregnant, particular attention should be paid to the possible occurrence of pheochromocytoma which is a high risk for both mother and baby. We were recently confronted with the case of such a patient who had increased catecholamine excretion and adrenal medullary hyperplasia before and during pregnancy.

The patient, a 29-year-old woman with MEN 2A (mutation at codon 634) had a thyroidectomy for MTC at the age of 21. Her grandmother, her mother and two uncles had already suffered from MTC, hyperparathyroidism and bilateral pheochromocytoma. She consulted with the aim of getting pregnant. So, because of her age, we did not discourage her in this project providing she had a thorough check-up beforehand. She only complained of occasional spells of nervousness but without palpitation and with normal blood pressure. Apart from levothyroxine, she denied the use of any other medication. Clinical examination was unremarkable. Blood

pressure was 105/70 mmHg and pulse 72/min. Blood results were as follows: free T4 1.23 ng/dl (normal: 0.7-1.48), TSH 2.76 µU/ml (normal 0.35-4.94), calcitonin 2.5 pg/ml (normal 0-10) and chromogranin 1.6 U/l (normal < 23). A 24-hour urine collection revealed a normal excretion of adrenaline, noradrenaline, dopamine, vanillylmandelic acid and homovanillylmandelic acid but increased metadrenaline and normetadrenaline which were 1.87 (normal ≤ 1.75) and 2.31 µmol/24 hour (normal ≤ 2.13) respectively. Catecholamines were measured by high-performance liquid chromatography with electrochemical detection. <sup>123</sup>I-Metaiodobenzyl guanidine scintigraphy showed an increased uptake of the tracer in both adrenals but with predominance on the left side. A Computed Tomographic scan confirmed left adrenal hyperplasia (12 x 16 x 28 mm). Results of the investigations were explained to the patient and her partner as well as the risks of pheochromocytoma during pregnancy and the possible transmission of the RET mutation to the baby. The potential of recent technology (prenatal molecular diagnosis of RET mutation by amniocentesis, in vitro fertilisation and the pre-implantation genetic diagnosis) was also clearly presented. The couple dismissed the idea of special procedures, willing to have a natural pregnancy. The patient also considered MEN 2A as something common in her family and to live with without anxiety. Follow-up of the pregnancy in concert with the obstetrician was uneventful. Blood pressure remained normal during pregnancy while metadrenaline and normetadrenaline excretion remained elevated (Figure 1). The patient dismissed a caesarean section. Thus, a vaginal delivery was planned at 39 weeks of pregnancy according to the obstetrical conditions. The patient gave birth under an epidural and after oxytocin infusion which was started in the morning. She had a normal vaginal delivery in the evening, the baby being in very good health. Blood pressure remained normal throughout the day with measurements ranging from 120/60 to 130/80 mmHg. No spells of tachycardia were noted throughout the day and no anti-hypertensive drugs were



**Figure 1:** Twenty-four hour urine metadrenaline (MA) and normetadrenaline (NMA) 4.5 months before pregnancy, during pregnancy and 5 weeks after delivery. Horizontal dotted lines indicate the upper limit of normal range. Blood pressure (measured regularly by the patient at home) remained normal throughout pregnancy with average values of 120/70 mmHg.

needed. Blood pressure remained normal on the next four days. One month after delivery, 24-hour excretion of catecholamines and their metabolites were normal, including metadrenaline and normetadrenaline.

In conclusion, this case of MEN 2A illustrates that normal pregnancy and delivery are still possible at a stage of adrenal medullary hyperplasia associated with moderate catecholamine hypersecretion. The situation would have been different in the case of overt pheochromocytoma which conventionally requires surgery during pregnancy (3, 4). The timing, however, remains a controversial issue. In the only recent review (six cases over a period of 25 years), the investigators

recommend a resection of pheochromocytoma before 24 weeks of gestation (4). After 24 weeks, surgical removal is recommended after an elective caesarean section. Vaginal delivery is considered as more dangerous than caesarean section. Of note, RF Gagel (3) reports the management of a patient with pheochromocytoma through a successful pregnancy and delivery under adrenergic antagonism, which will remain an exception due to unusual circumstances.

Before envisaging a pregnancy, a genetic prenatal RET testing is also important to consider in families with a suspicion of a hereditary cause of pheochromocytoma, such as MEN 2A (4, 5). In MEN 2A, pheochromocytoma tends to occur later (after MTC). We would thus advise starting pregnancy as early as possible and under careful and collaborative monitoring by the obstetrician and the endocrinologist. It is also important to take into account psychological and ethical dimensions. Before and during pregnancy, our patient was fully serene and reassured thanks to the close and long-term interest of the whole family including the grandmother, still in good shape 30 years after surgery for MTC, bilateral pheochromocytoma and hyperparathyroidism. Regular personal contact with medical staff fully available and attentive for several years certainly plays a key role to create an excellent atmosphere and the confidence of the patient with such a chronic and difficult disease.

## REFERENCES

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