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MEN2B and Pregnancy

Pheochromocytoma in pregnancy: **diagnosis**

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- Catecholamine metabolism is generally unaltered during healthy pregnancy
  - In patients with preeclampsia, plasma catecholamine levels are only slightly increased.
- Most reliable test: plasma and/ or 24-h urine (nor)metanephrine
- Imaging of choice: ultrasound and MRI

Eur J Endocrinol. 2017;177: R49–R58.

Pheochromocytoma in pregnancy: **treatment**

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- In pregnant patients, target BP is not known.
- Both an excess of catecholamines as well as relative hypotension can reduce uteroplacental circulation.
- Balance between Rx HT vs. maintaining adequate uteroplacental circulation
- Pregnant patients with normal BP should be treated with low-dose α-adrenergic blockers as well to prevent paroxysmal peaks in BP.

Eur J Endocrinol. 2017;177: R49–R58.

Pheochromocytoma in pregnancy: **medication**

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Medication	Class	Category	Caution
Phenoxybenza-mine	α-adrenergic receptor blockers	C	Pass placenta Report: neonatal hypotension, respiratory depression
Doxazosin	α-adrenergic receptor blockers	C	May cross placental No report of neonatal hypotension and respiratory depression
Prazosin	α-adrenergic receptor blockers	C	Data of more neonatal death as treatment for hypertension in pregnancy compare to nifedipine*
Propranolol Metoprolol	β-Adrenergic receptor blockers	C	Associated with intrauterine growth restriction Generally advised to use only for a short period
Nifedipine	Calcium channel blockers	C	Generally thought to be safe during pregnancy

*BJOG. 2000;107(6):759-765
Eur J Endocrinol. 2017;177: R49–R58.

Pheochromocytoma in pregnancy: CAUTION

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- **Labetalol** (combined alpha- and beta-blocker) has relatively weak alpha blockade resulted in paroxysmal hypertension in several cases
  - No longer recommended
- **Methyldopa:** worsen hypertension in pheochromocytoma
  - Not recommended
- **Avoid drug-induced pheochromocytoma crisis**
  - Corticosteroids, opioids, metoclopramide, thiopental, ketamine, ephedrine and muscle relaxants

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Pheochromocytoma in pregnancy: **Surgery**

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- Recommend to remove the tumor in the 2nd trimester
- In the 3rd trimester, when medical pretreatment is sufficient, it is generally recommended to postpone resection till after delivery
  - Enlarged uterus diminishes accessibility of the tumor
  - Adrenalectomy can be scheduled in the same session or at a later time several days to weeks after delivery.
- Right lateral position for left adrenal extirpation increases the risk for IVC compression
  - increasing the risk of uteroplacental hypoperfusion during surgery

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Pheochromocytoma in pregnancy: **delivery**

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Normal labor

- The period of active pushing and stress during the second stage of labor can be shortened or even be avoided by performing an instrumental vaginal delivery.
- Oxytocin and other uterotonic medication should be used with caution.

Cesarean section:

- Potentially stressful due to excessive blood loss due to the uterine incision and a catecholamine excess by manipulation of the peritoneum or the tumor.

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MEN2B

MEN 1	MEN 2A	MEN 2B
Pituitary adenoma		Mucosal neuromas
Parathyroid hyperplasia	Parathyroid hyperplasia	Marfanoid body habitus
	Medullary thyroid carcinoma	Medullary thyroid carcinoma
Pancreatic tumors	Pheo-chromo-cytoma	Pheo-chromo-cytoma

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The Steinberg sign
This test is used for the clinical evaluation of Marfan patients.

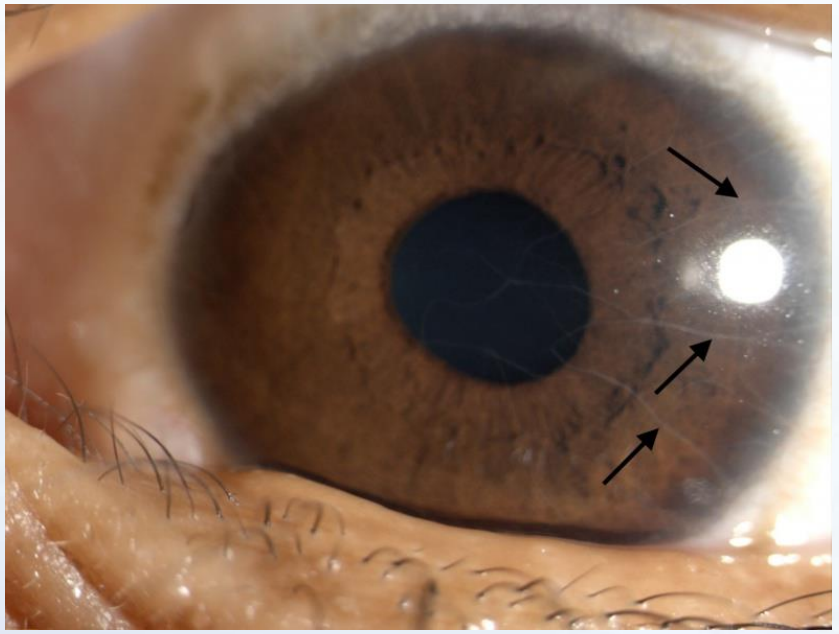
Fold your thumb into the closed fist. This test is positive if the thumb tip extends from palm of hand.

The Walker-Murdoch sign
This test is used for the evaluation of patients with Marfan syndrome.

Grip your wrist with your opposite hand. If thumb and fifth finger of the hand overlap with each other, this represents a positive Walker-Murdoch sign.

MEN2B: ocular feather

- Prominent corneal nerves appear as fine, branching, linear, stromal opacities that extend from the limbus to the central cornea.
- MEN2B should be ruled out in any patient with prominent corneal nerves, especially if there are additional suggesting ocular and systemic features present.
- Other conditions that can present with prominent corneal nerve, such as MEN2A, NF1, and leprosy.



Slit-lamp photograph demonstrating prominent corneal nerves (arrows) in a patient with MEN2B. Courtesy of Dian Petrus van der Westhuizen,MBChB

Graefes Arch Clin EXP Ophthalmol. 2001;239(5):391-394.

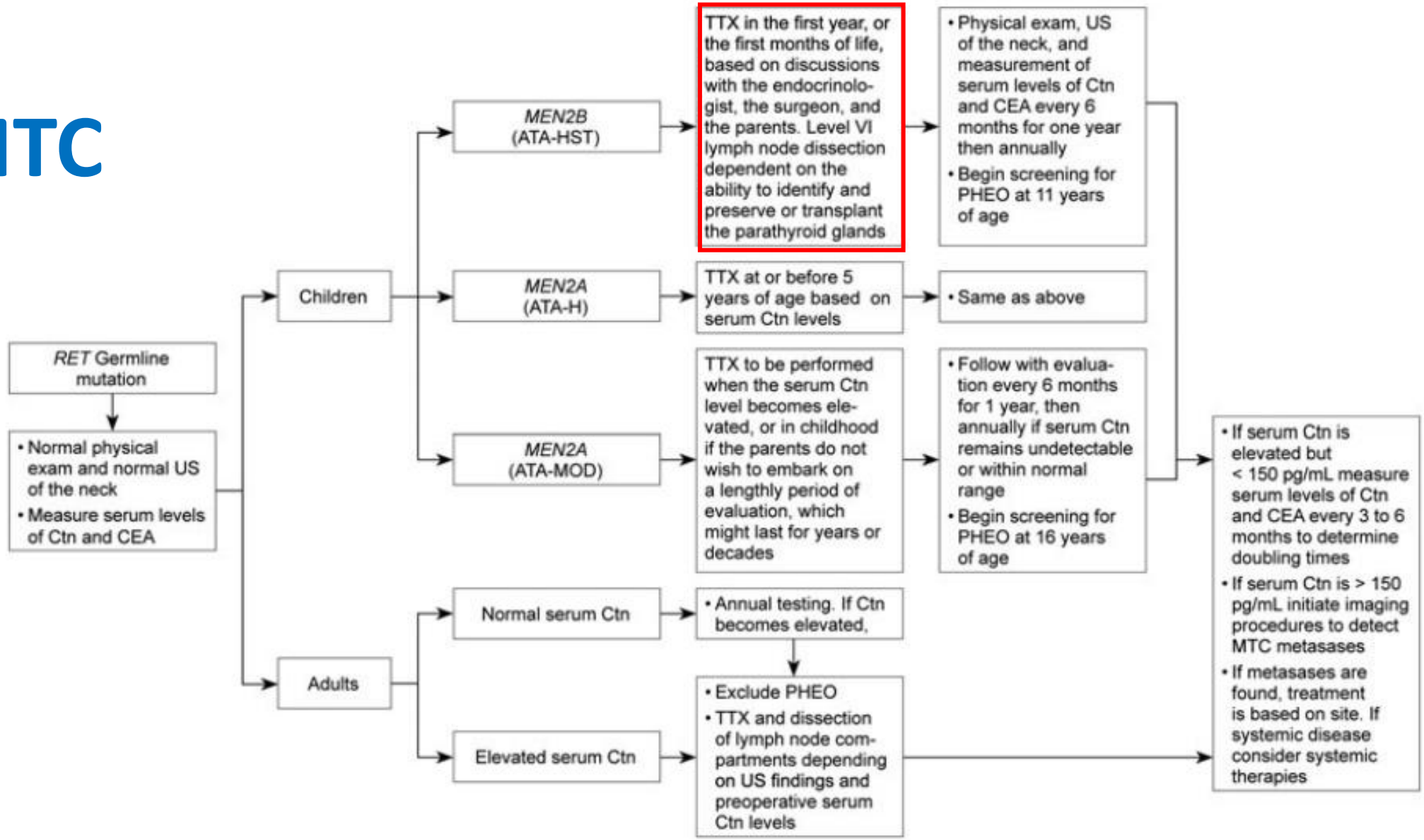
Medullary thyroid carcinoma

TABLE 4. RELATIONSHIP OF COMMON *RET* MUTATIONS TO RISK OF AGGRESSIVE MTC IN MEN2A AND MEN2B, AND TO THE INCIDENCE OF PHEO, HPTH, CLA, AND HD IN MEN2A

RET *mutation*[a]	*Exon*	*MTC risk level*[b]	*Incidence of PHEO*[c]	*Incidence of HPTH*[c]	*CLA*[d]	*HD*[d]
G533C	8	MOD	+	–	N	N
C609F/G/R/S/Y	10	MOD	+/++	+	N	Y
C611F/G/S/Y/W	10	MOD	+/++	+	N	Y
C618F/R/S	10	MOD	+/++	+	N	Y
C620F/R/S	10	MOD	+/++	+	N	Y
C630R/Y	11	MOD	+/++	+	N	N
D631Y	11	MOD	+++	–	N	N
C634F/G/R/S/W/Y	11	H	+++	++	Y	N
K666E	11	MOD	+	–	N	N
E768D	13	MOD	–	–	N	N
L790F	13	MOD	+	–	N	N
V804L	14	MOD	+	+	N	N
V804M	14	MOD	+	+	Y	N
A883F	15	H	+++	–	N	N
S891A	15	MOD	+	+	N	N
R912P	16	MOD	–	–	N	N
M918T	16	HST	+++	–	N	N

Thyroid. 2015 ; 25(6): 567–610

MTC



Thyroid. 2015 ; 25(6): 567–610

Management in MTC with distant metastasis

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- No role of radioactive Rx
- Surgery, RF ablation, chemoembolization, radiation therapy
- Systemic therapy:
  - Multitarget Kinase Inhibitors (MKIs): vandetanib and cabozantinib Rx first-line Rx for advanced MTC.
    - Could also be used for RET-altered malignancies.
  - Selpercatinib is highly selective receptor tyrosine kinase RET inhibitor, US FDA approved in 2020.
- Peptide Receptor Radionuclide Therapy (PRRT)

Expert Rev Anticancer Ther. 2023;23(9):943-957.