Male Fertility in Cystinosis

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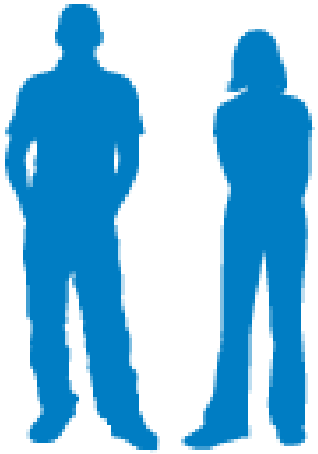
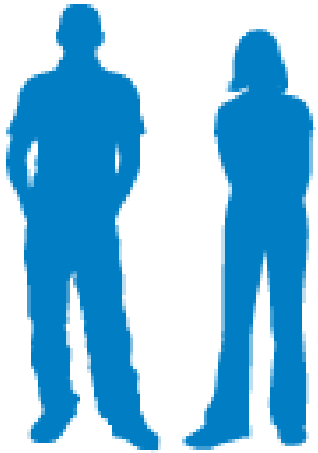
Cystinosis
Evolution into a treatable chronic disorder



Cysteamine

Questions & challenges faced by cystinosis patients and researchers

Longer life expectancy
Better quality of life



Challenges

Long-term complications

New therapies
(stem cell-based gene therapy)

Fertility – Wish having children

Cysteamine

Fertility: what's in a name?

"Natural capability to produce offspring"

1. **Anatomy** (Puberty)
2. **Function**: production of
- 'gametes' (egg cells, sperm cells)
- sexual hormones (estrogen, progesterone, testosterone)
3. Feedback loops: **Brain - Sexual organs communication**

+

4. Other factors: sexual behavior, nutrition, timing, culture, economics, way of life, emotions …

Previous fertility studies in cystinosis

Earlier

Fertility was not investigated

Nowadays

Advances in management:

- Females: fertile (*Reiss et al. 1988*)
- Males: infertile + azoospermic

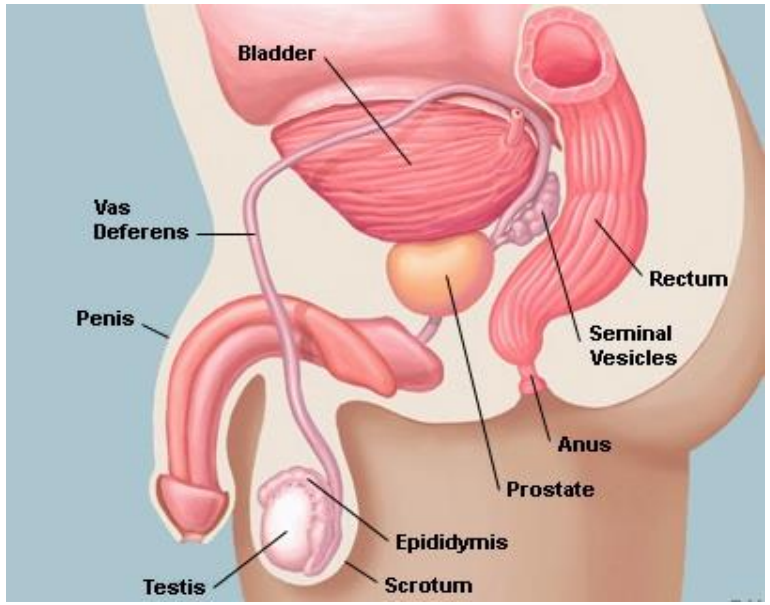
(Chik *et al.* 1993 ; *Besouw et al. 2010*)

Recently

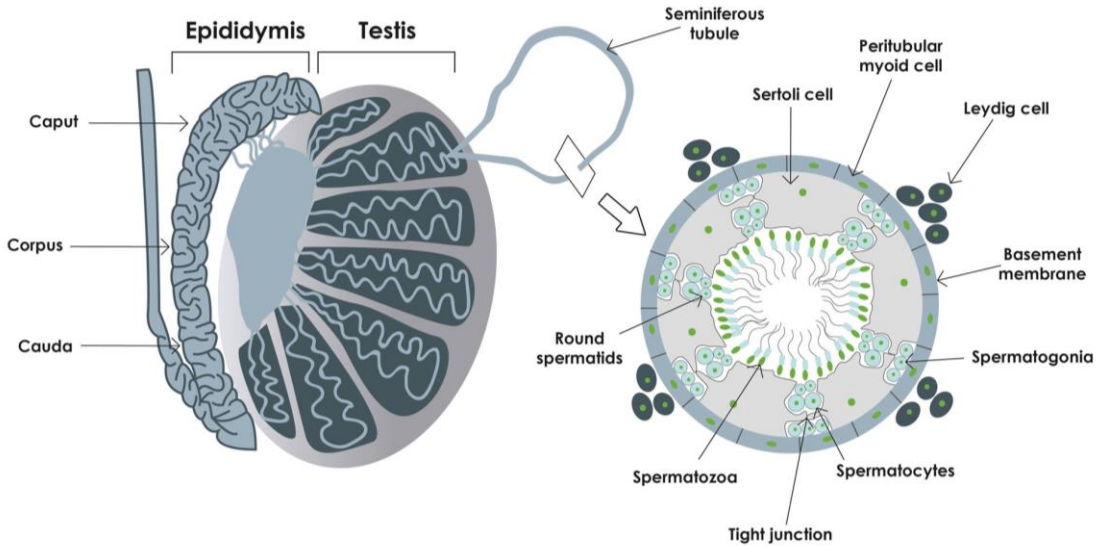
First successful conception by male cystinosis patient (*Veys et al. 2017*)

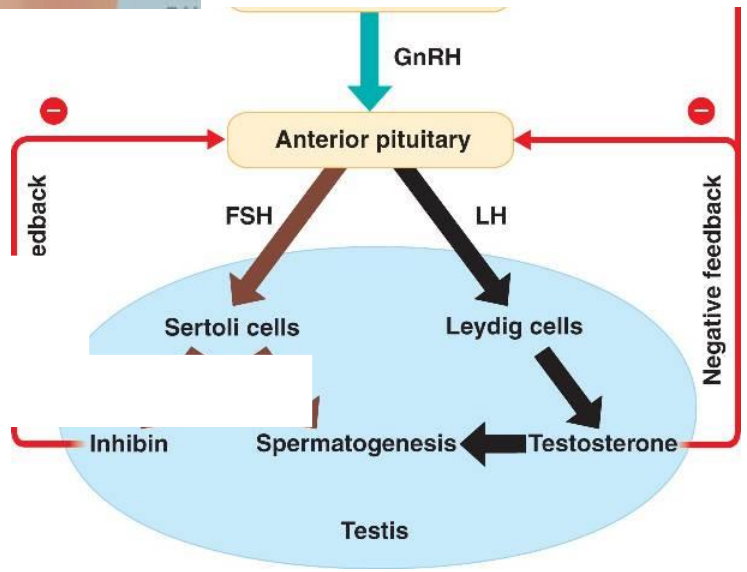
Male Fertility

Anatomy



Function

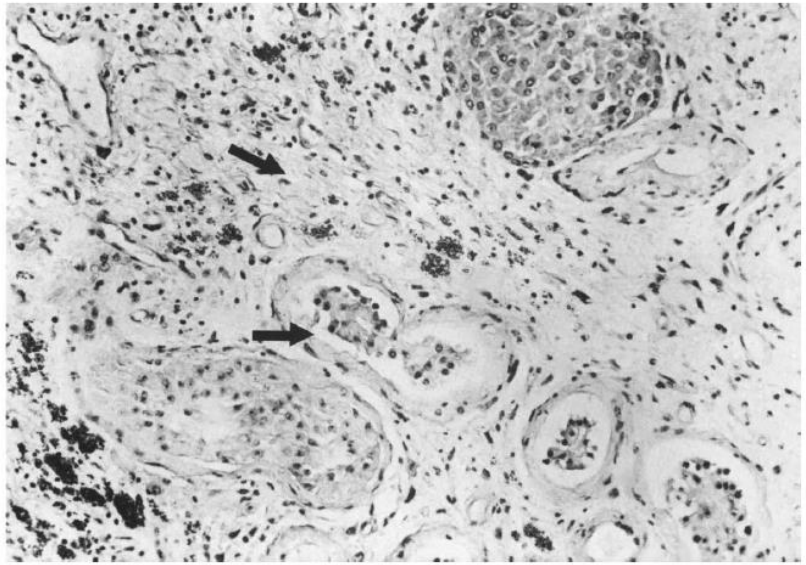




Communication
Brain – Sexual organs
Feedback

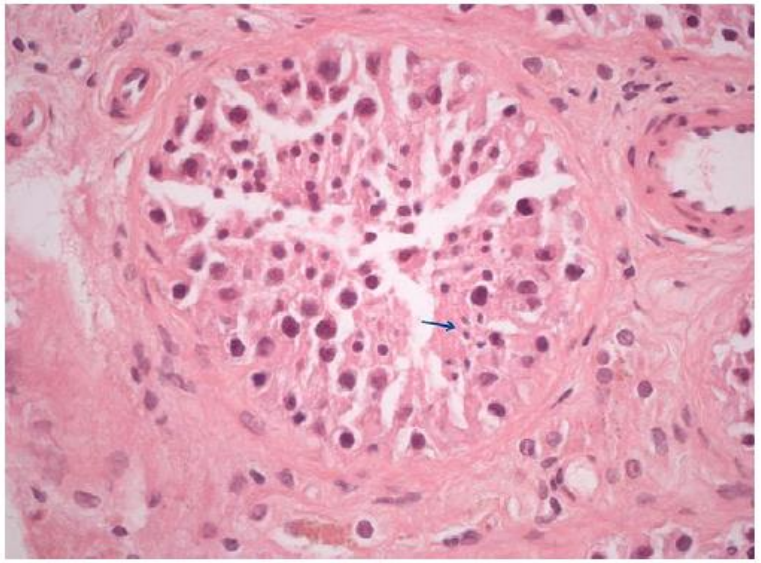
Histology studies in male cystinosis patients

Chik *et al.* 1993



Cystinosis patient in advanced stage of disease, not well treated with cysteamine: **fibrotic testes**

Besouw *et al.* 2010



Young cystinosis patient treated with cysteamine: **normal testes, but no sperm cells in ejaculate = azoospermia**

Retrospective analysis of fertility in cystinosis male patients

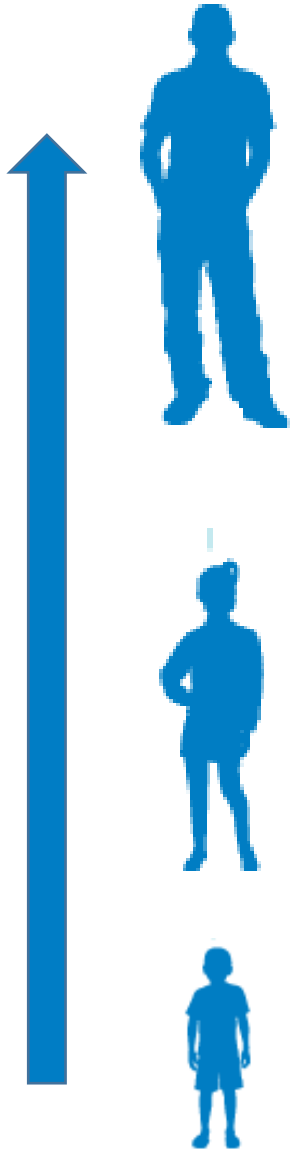
	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age at sampling	16	27	33	27	24
Diagnosis	Infantile cystinosis	Infantile cystinosis	Infantile cystinosis	Infantile cystinosis	Infantile cystinosis
Johnsen Score	8-9	7-8	8-9	Not performed	Not performed
Testicular sperm	Yes	Yes	Yes	Not performed	Yes
Epididymal sperm	Not performed	Not performed	Not performed	Yes	Yes
Sperm count	Not performed	Azoospermia	Azoospermia	Azoospermia	Azoospermia
Plasma testosterone (N.R. 11.0-45.0 nmol/L)	18.0	8.7	22.2	17.0	Not available
Plasma LH (N.R. 1.7-8.6 IU/L)	4.6	12.3	9.6	7.3	Not available
Plasma FSH (N.R. 1.5-11.0 IU/L)	5.9	28.7	7.3	8.4	Not available

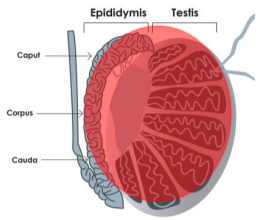
Cause for azoospermia in male cystinosis patients ?

Early Adulthood

- *Normal sperm production in testes*
- *(Sub)normal sex hormone levels*
- *(Mostly) no sperm cells in ejaculate in patients with* ***infantile cystinosis***
- *Reduced number of sperm cells in ejaculate in patients with* ***juvenile cystinosis***
- *Normal sperm count in patients with* ***ocular cystinosis***

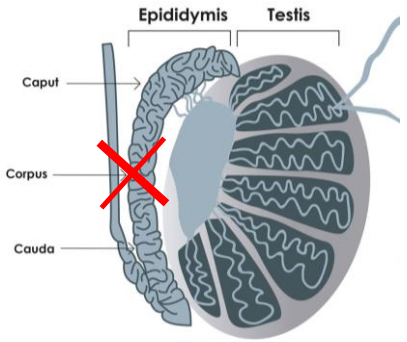
Reda, Veys *et al*. JIMD 2021





Later Adulthood

- *Smaller testicular volume*
- *Reduced sperm production*
- *Low levels of sex hormones*
- *No sperm cells in ejaculate*



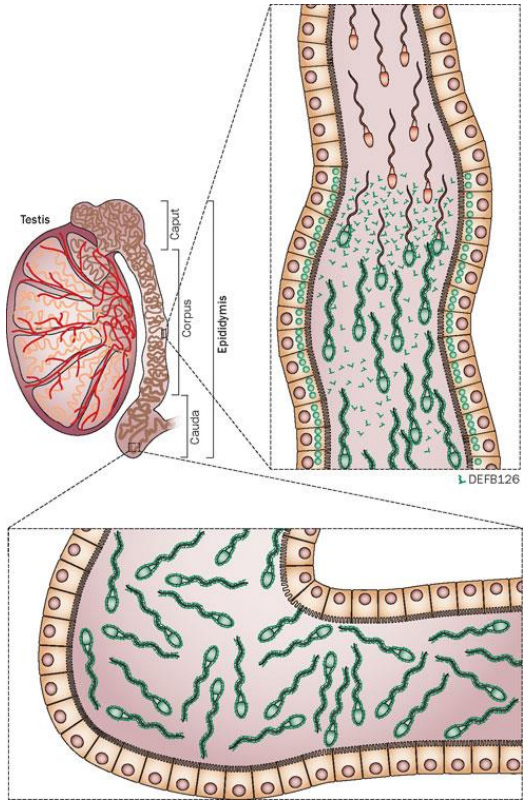
? Problem at epididymis level?

Epididymis and fertility

Epididymis is crucial for :

- Sperm **maturation**
  (motility and fertilizing capacity)
- Sperm **storage**

- Fluid & ions **reabsorption**

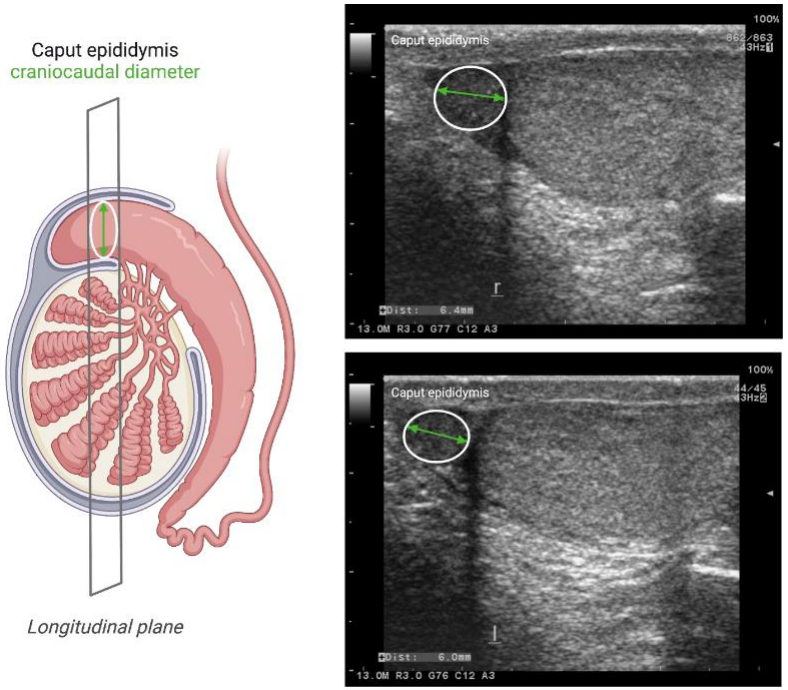


Prospective semen analysis in cystinosis patients

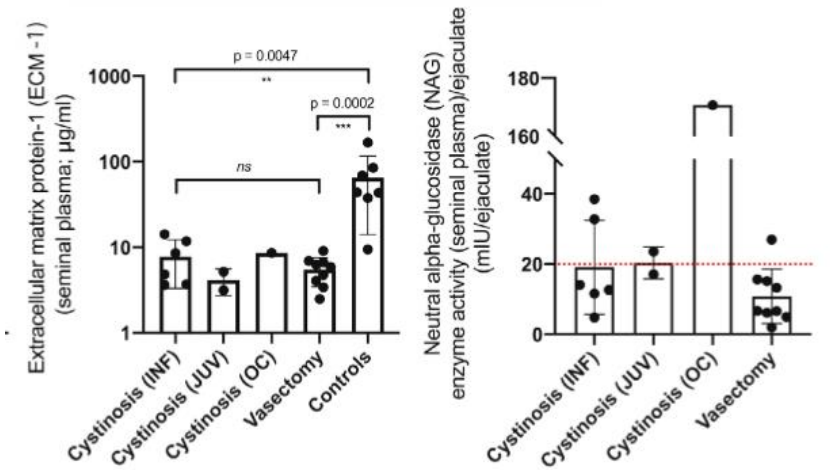
Participants	Number of individuals	Semen analysis
Healthy control	7	Normospermia (>20 million/ml)
Vasectomy control	9	Azoospermia (0/ml)
Ocular cystinosis	1	Normospermia (>20 million/ml)
Juvenile cystinosis	2	Oligospermia (<20 million/ml)
Infantile cystinosis	5	Azoospermia (0/ml)
Infantile cystinosis	1	Oligospermia (<20 million/ml)

Cystinosis is associated with epididymis dysfunction

1. Enlargement of caput epididymis



2. Reduced concentration of epididymis markers in ejaculate



3. Altered gene expression profile in CTNS – deficient epididymis cells

Rohayem et al. 2021: reduced fructose and Zn concentrations in ejaculate

Reda, Veys et al. 2021

Reda, Veys, Besouw 2022

Cysteamine and fertility

- **<u>Direct effect (high concentration):</u>** spermicidal

  (*Swami et al. 2017*)

- **<u>Indirect effect (rat):</u>** Upregulation of ghrelin

  (*Fukuhara et al. 2005*)

  → ↓ gonadotropin

  → ↓ testosterone

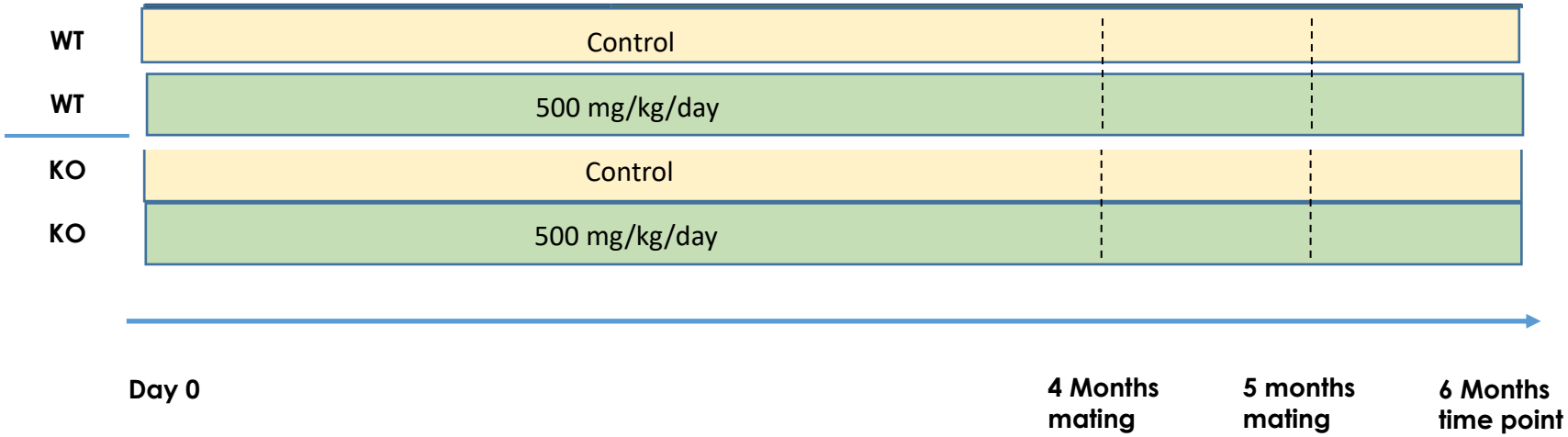
Possible negative impact on spermatogenesis and fertility

Effect of cysteamine on fertility: animal study

Wild-type (WT) and *Ctns* knockout (KO) mice:

- Cysteamine treatment versus no treatment

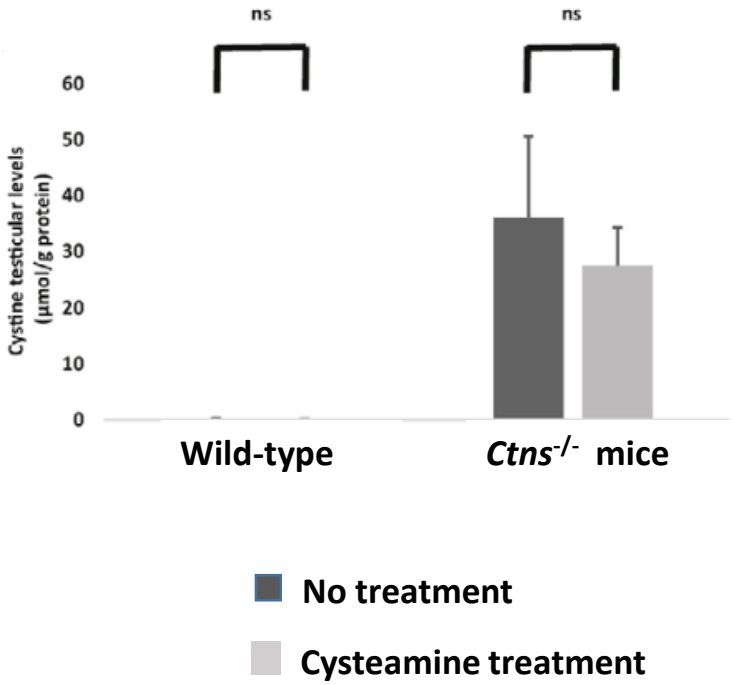
- Study of hormonal levels, sperm count, testes morphology, capacity to have offspring



Conclusion: **Cysteamine does not negatively affect the investigated fertility parameters in male mice (wild-type and *Ctns*$^{-/-}$)**

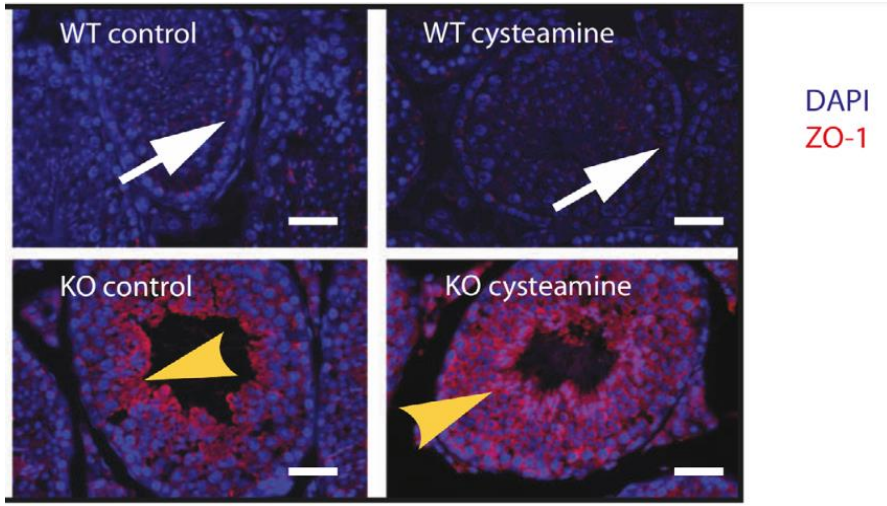
Can cysteamine improve fertility?

1. No effect on cystine accumulation in testes

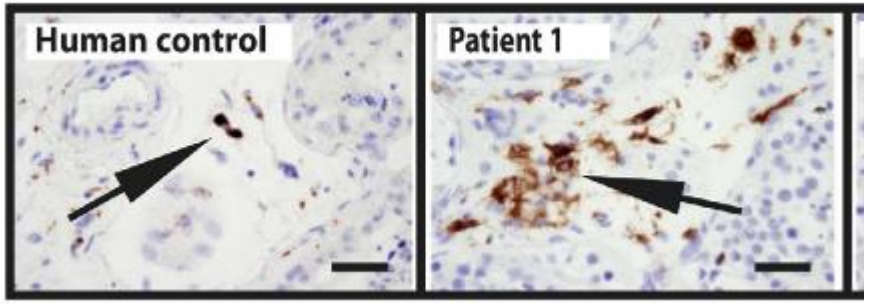


Reda & Veys et al. 2021

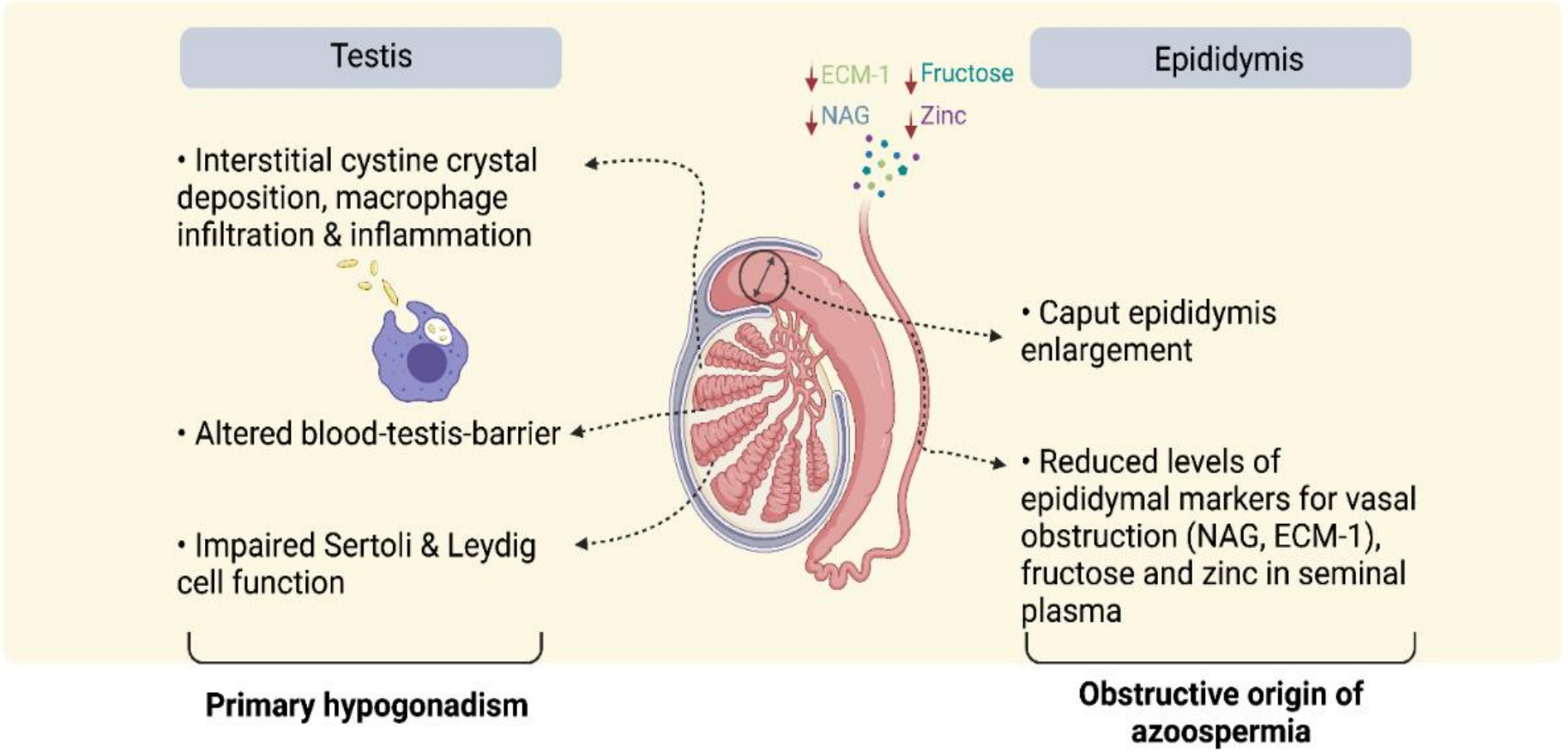
2. No restoration of altered blood - testes barrier



3. No effect on macrophage infiltration (CD68 staining)



Mechanism of infertility in cystinosis



Treatment recommendations

- Investigation of fertility & preservation of sperm in young adult cystinosis males
- ICSI procedure in males with azoospermia is possible
- Effect of other than cysteamine treatment options?

Reda, Veys, Besouw 2022

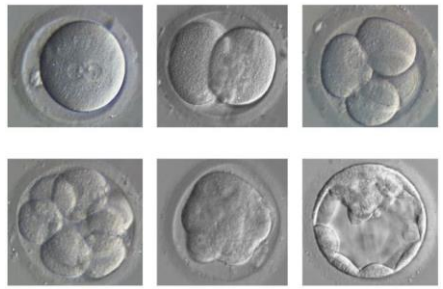
First successful conception induced by a male cystinosis patient

First Successful Conception Induced by a Male Cystinosis Patient

Koenraad R. Veys • Kathleen W. D'Hauwers • Angelique J. C. M. van Dongen • Mirian C. Janssen • Martine T. P. Besouw • Ellen Goossens • Lambert P. van den Heuvel • Alex A. M. M. Wetzels • Elena N. Levtchenko

PESA
Percutaneous Epididymal Sperm Aspiraton

ICSI
IntraCytoplasmic Sperm Injection



Fertilization & Development of embryo ‘in vitro’

Take Home Message - Male fertility in cystinosis

1. Majority of infantile nephropathic cystinosis patients show an absence of sperm cells in the ejaculate (azoospermia), however some young patients may show oligospermia

2. Juvenile nephropathic cystinosis patients show an oligospermia, are fertile and are able to have an offspring

3. **Cysteamine does *not* affect fertility**

4. In young cystinosis patients, semen analysis is always useful

5. Cryopreservation of sperm should always be considered in young male cystinosis patients

6. **Having an offspring naturally (juvenile phenotype) or by assisted reproductive techniques (ART; ICSI) is possible in male cystinosis patients!**

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