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Pregnancy & fertility in CML while using TKIs: what's new?

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Overview

- Male patients
- Women diagnosed in pregnancy
- Women who wish to have children on treatment for CML

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TKI, men and offspring

>200 pregnancies reported in partners of men on imatinib

- No suggestion of any problems in conception, pregnancy, delivery. Congenital abnormalities (n=3) same as background

>72 pregnancies in partners of men on dasatinib

- Spontaneous abortions (n=2), one infant with syndactyly

>41 pregnancies in partners of men on nilotinib

- one termination for fetal abnormalities

17 pregnancies in partners of men on bosutinib

- 9 live births, 1 spontaneous and 4 elective terminations

22 pregnancies in partners of men on ponatinib: 10 healthy infants, 9 unknown outcome, one miscarriage with fetal abnormalities, two additional miscarriages

Pye et al. Blood 2008, Cortes et al, Am J Hematol, Novartis IB. Cortes et al ESH iCMLf, 2018.

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TKI and fertility in female animal models

- No effects on fertility at tested doses in females for imatinib, bosutinib, dasatinib, nilotinib or ponatinib
- When administered to pregnant animals, caused death of litter. Abnormalities of skeleton, brain, gastrointestinal tract and kidneys seen with all drugs
- Thought to be due to inhibition of another tyrosine kinase – the platelet derived growth factor receptor (PDGFR)

Investigator brochures for all tyrosine kinase inhibitors

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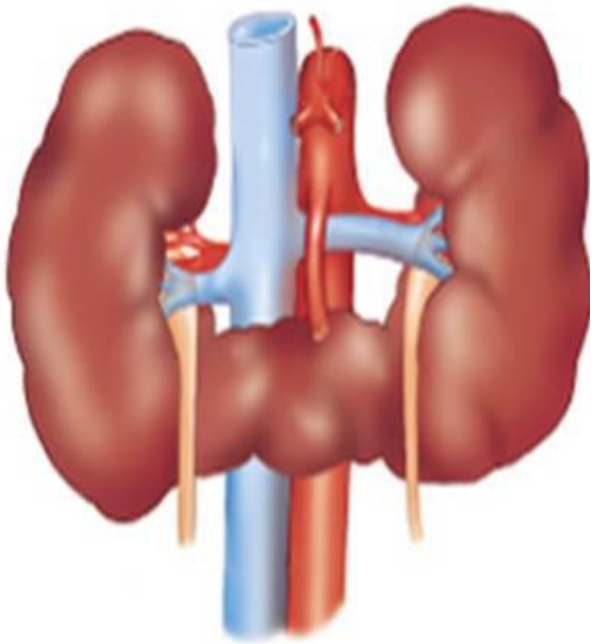
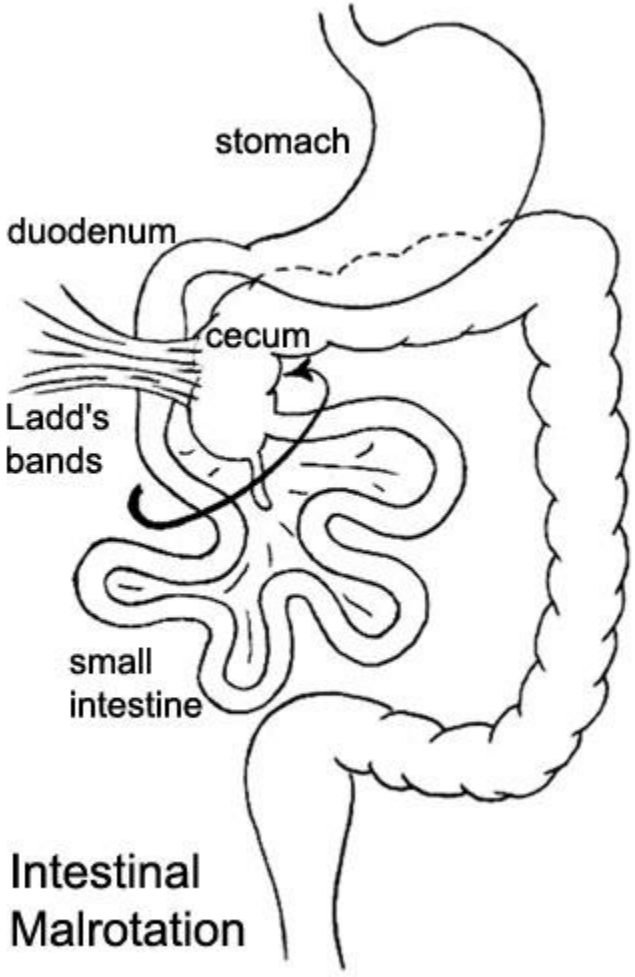
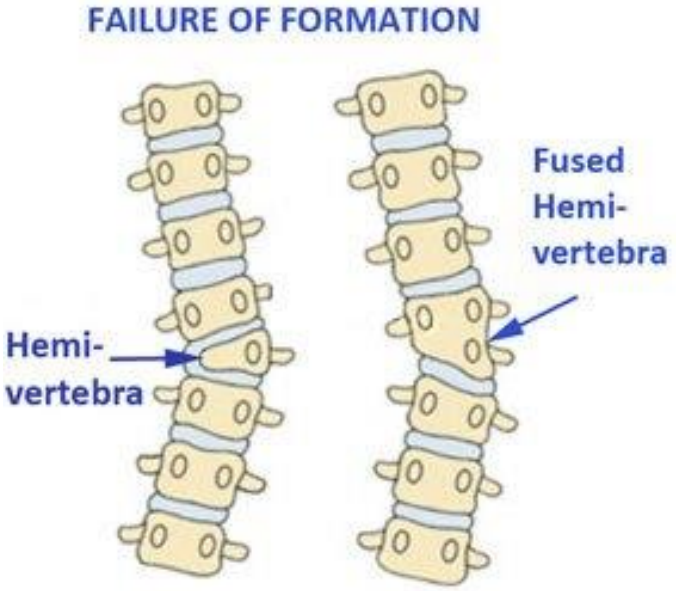
Examples of congenital malformations



Horsehoe kidney



Intestinal Malrotation



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Imatinib in Pregnancy

125 pregnancies reported on imatinib with known outcomes

- Most stopped imatinib on discovering pregnancy
  - 50% live births
  - 14% spontaneous abortion
  - 9% congenital abnormalities similar to those seen in the animal studies

- Effect thought to be in the first trimester as organs develop

Pye et al. Blood. 2008; 111(12): 5505-5508.

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Other TKIs in pregnancy

78 pregnancies reported on dasatinib, known outcome for 46:

- 20/46 (43%) live births; 15 (33%) normal term infants, 8 miscarriages & 18 terminations
- 7/46 (15%) congenital abnormalities; 2 identified at birth and 5 after elective termination, 2 with hydrops fetalis (dasatiinib in 2nd trimester in one)

50 pregnancies on nilotinib

- 3/45 congenital abnormalities (omphocoele, cardiac defects)

16 pregnancies on bosutinib: outcome known for 11

- 6 live births, 5/6 known to have discontinued in 1st trimester
- 3 terminations and 1 miscarriage

Cortes et al, Am J Hematol. 2015, Expert Rev Hematol. 2016 Aug;9(8):781-91, Cortes et al, ESH iCMLf meeting 2018

CML diagnosed in pregnancy

- Experience relatively limited as median age of onset 60-65 yrs
- Diagnosis in < 1 per 100,000 pregnancies
- Disease may be detected very early so treatment not required
- Main considerations
  - Disease phase
  - Gestational age
  - Blood counts

Milojkovic et al, Blood 2013

CML diagnosed in pregnancy

If treatment required options to be considered (and perhaps dismissed) include

- **Leucapheresis**
- **Interferon**
- **Tyrosine kinase inhibitors**
- **Hydroxycarbamide**

Milojkovic et al, Blood 2013

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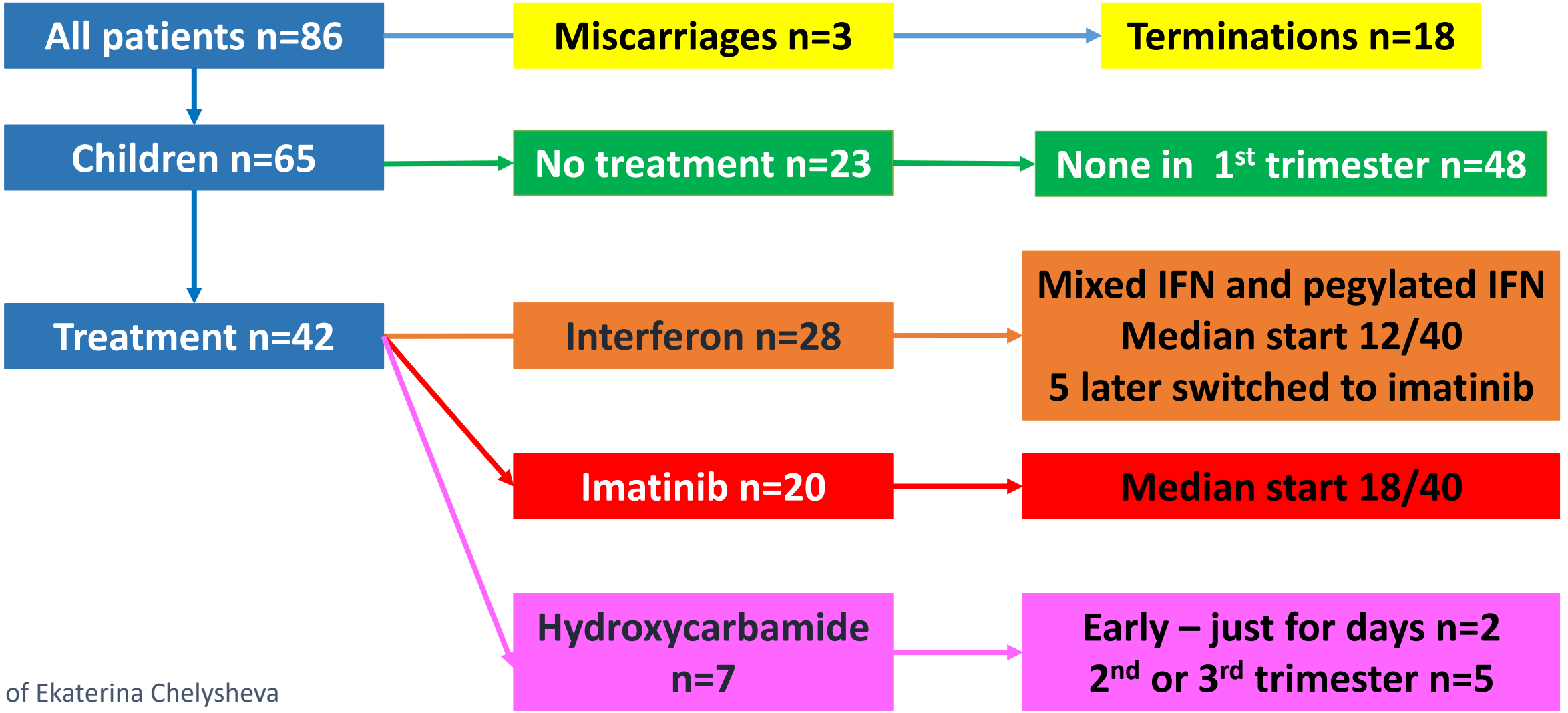
European Leukemia Net data: CML in pregnancy



Courtesy of Ekaterina Chelysheva

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European Leukemia Net data: CML in pregnancy

- 66 children (1 set of twins)
- 7 low birth weight – follow-up uneventful
- 2 mild congenital abnormalities
- Best response was at least major molecular remission in 65 of 75 with known data and at least 6/12 follow-up

- Imatinib thought to be safe in 3rd trimester and probably in 2nd – avoid in 1st trimester
- Dasatinib and nilotinib can cross the placenta and enter infant blood stream – avoid throughout pregnancy

Courtesy of Ekaterina Chelysheva

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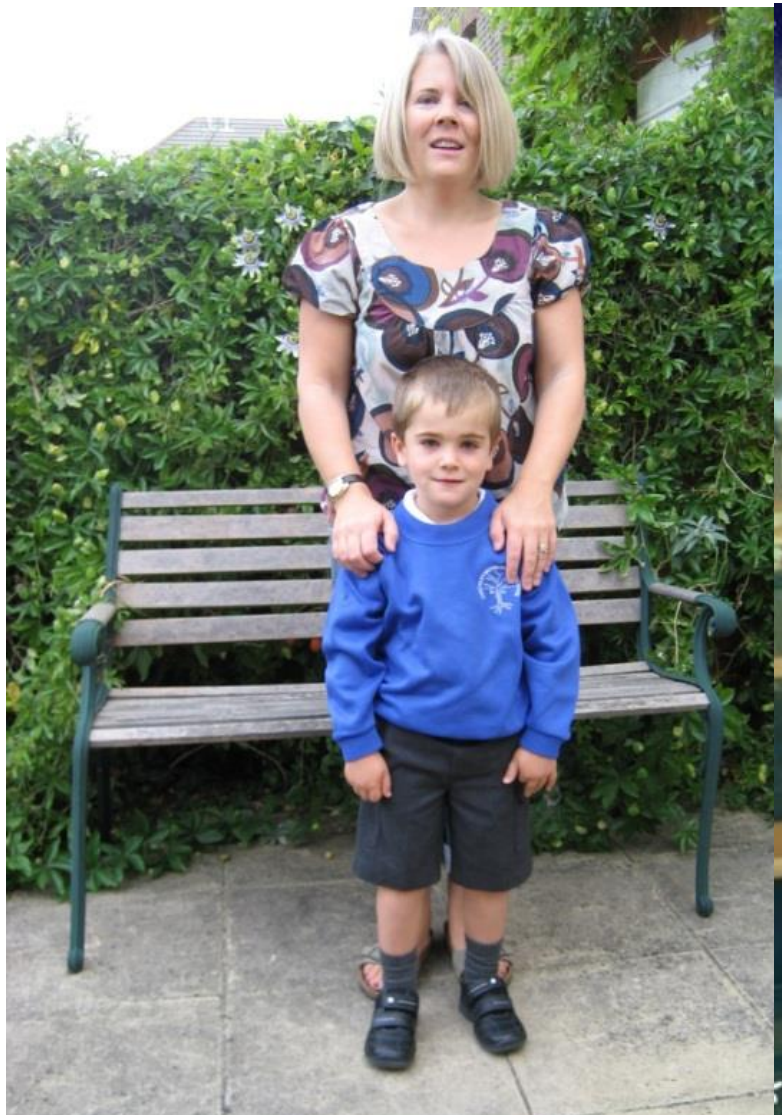
And it works!!!



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Women who wish to have children on treatment

- Very good responders
- Not so good responders
  - Age
  - Societal pressure
  - Unplanned

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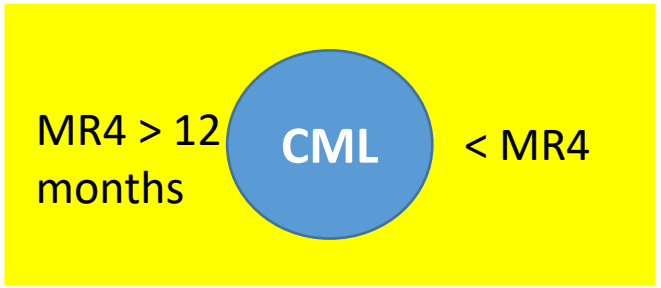
Planning a pregnancy

Remains in MR4: stay off TKI indefinitely irrespective of pregnancy

Becomes pregnant but loses MMR: Stay off TKI until delivery: use other strategies if necessary

Loses MMR & is not pregnant: re-start same or stronger TKI. Try again at later date



Recommend staying on TKI to get deeper response. Consider a more potent TKI

Substitute IFN for TKI, monitor closely and use other strategies if necessary

Refer for IVF, implant fresh embryos: use other strategies if necessary

IVF, freeze embryos: re-start more potent TKI and implant embryos when in MR4

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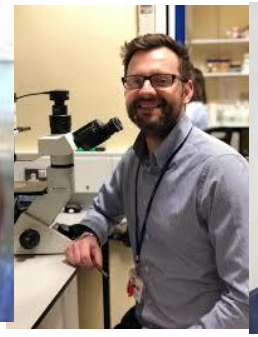

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