Imperial College London

Pregnancy and Fertility

Jane Apperley

Imperial College London

Different situations require different solutions

- **Men with CML on tyrosine kinase inhibitors**
- **Young men (pre-pubertal) with CML on tyrosine kinase inhibitors**
- **Women diagnosed with CML in pregnancy**
- **Women with CML on tyrosine kinase inhibitors**
- **Young women (pre-pubertal) with CML on tyrosine kinase inhibitors**

Imperial College London

Management of fertility in men

- **Men remain fertile throughout life**
- **Production of sperm begins 72 days before ejaculation, so effects of treatment last at least 10 weeks after last dose**
- **Stem cell transplantation usually renders men infertile**
- **Pre-TKI, cryopreserve sperm prior to any treatment**

Imperial College London

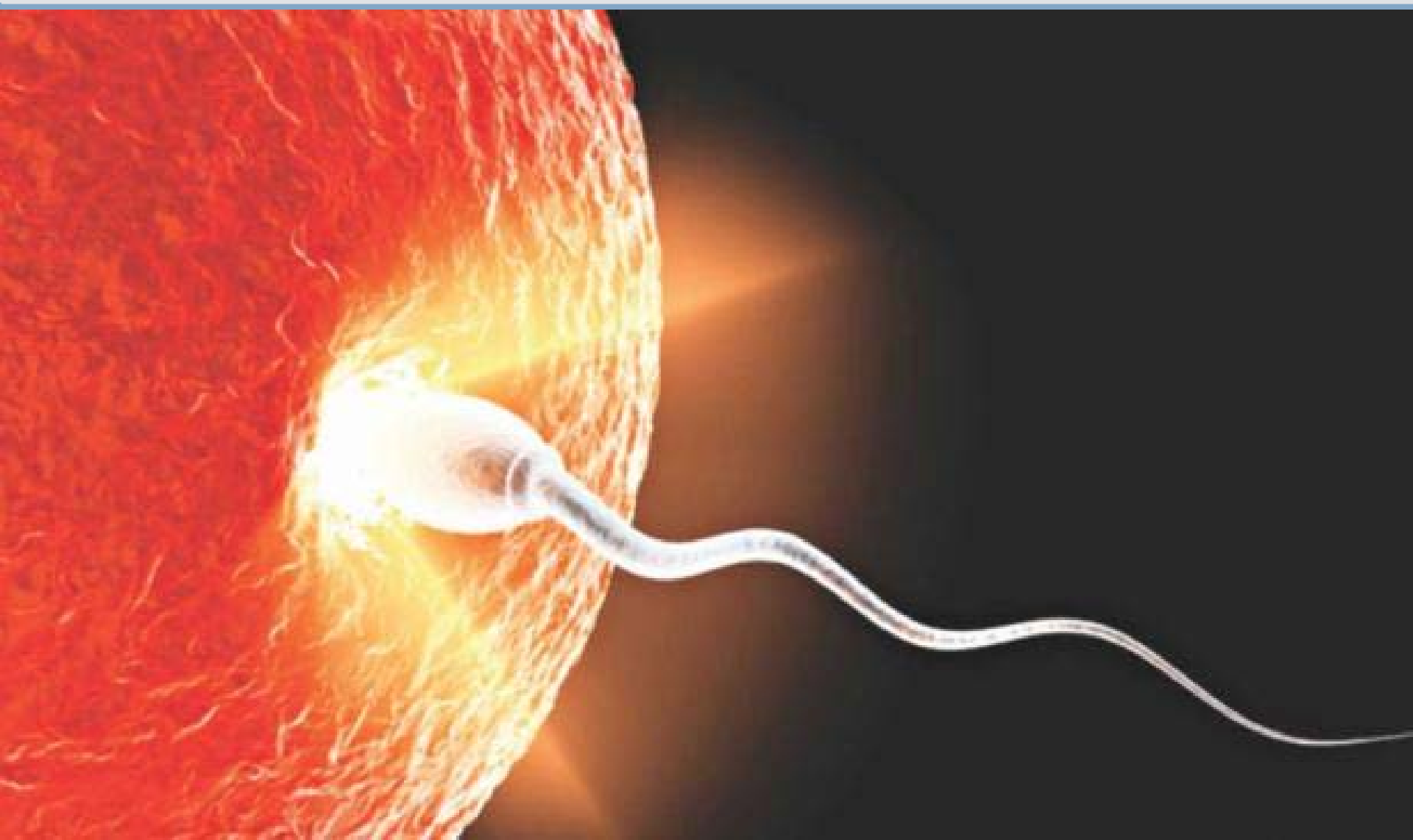
Tyrosine kinase inhibitors and fertility in men

- **No suggestion of any effect on sperm number and mobility in animal experiments**
- **French study of 71 men who stored sperm at diagnosis, compared with men donating for in vitro fertilisation techniques**
  - **Lower sperm counts**
  - **Higher percentage of abnormal sperm (71% vs 45%)**
  - **4 years later, 19/71 men had fathered 24 children – all normal**
- **Also studied 8 men after 16 (10-65) months on imatinib: similar to findings at diagnosis but not paired samples**
- **Recommended freezing sperm at diagnosis in all men**

Nicolini et al, 2016

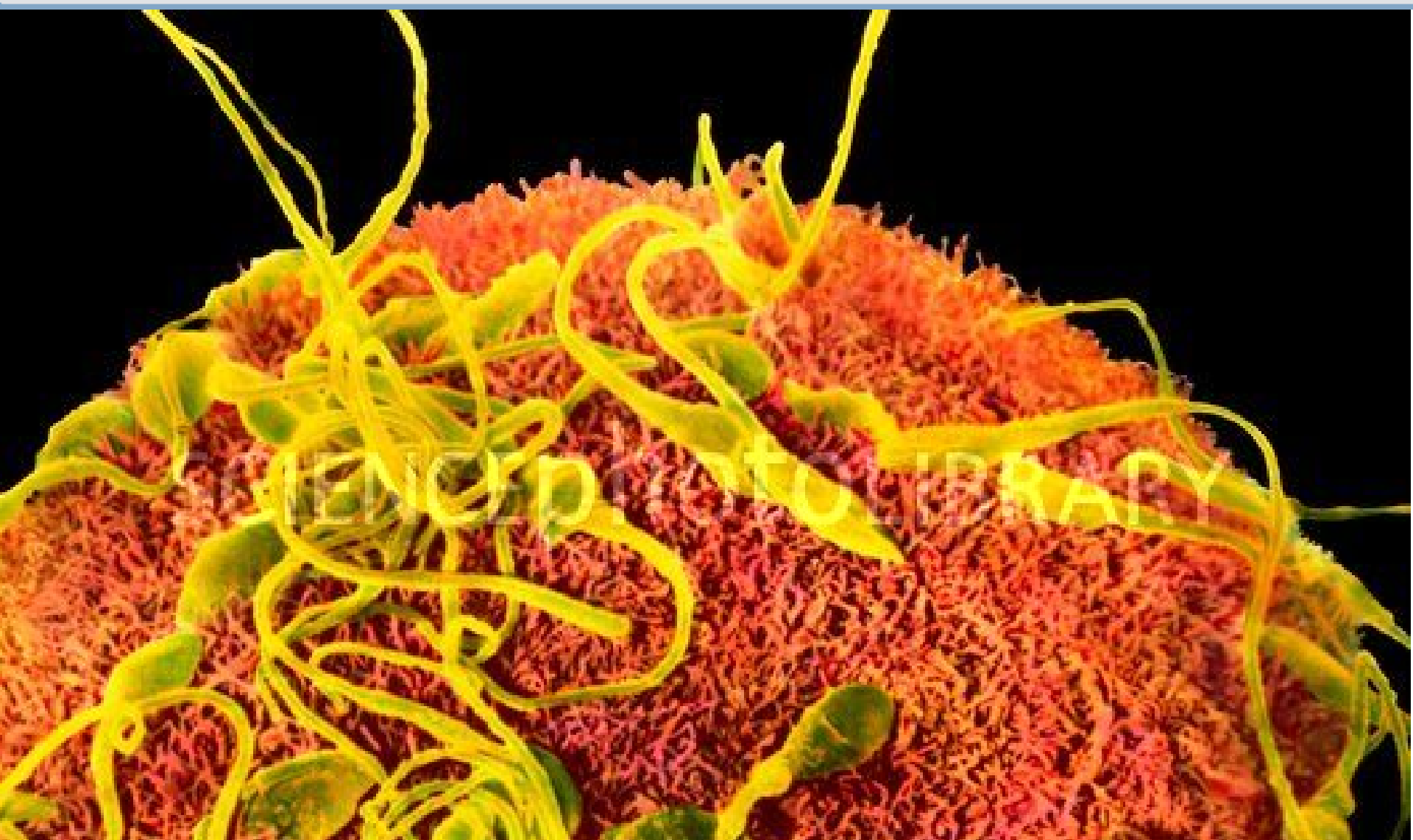
Imperial College
London

Fertilsation



Imperial College
London

Fertilisation



Imperial College London

Imatinib, men and offspring

- >200 pregnancies reported in partners of men on imatinib
- No suggestion of any problems in conception, pregnancy, delivery
- Some congenital abnormalities have occurred but at the same rate as in the non-CML population
  - one infant with malrotation of the small intestine,
  - one with congenital hip dysplasia
  - one stillbirth with malformations

Pye et al. Blood. 2008,.

Imperial College London

Dasatinib, nilotinib, bosutinib, men & offspring

- >72 pregnancies in partners of men on dasatinib
  - 2 spontaneous abortions
  - one infant with syndactyly

- >41 pregnancies in partners of men on nilotinib
  - one termination for fetal abnormalities
- 3 pregnancies in partners of men on bosutinib (all normal)
- None reported (so far) for ponatinib

Imperial College
London

Young men

Imperial College London

Techniques for younger males

- **Spermatogonial stem cell (SSC) transplantation, has been successful in mice but has not yet been applied in humans**
- **Transplantation of SSCs was first described in mice in 1994, generating full spermatogenesis in an otherwise infertile recipient mouse and functional sperm leading to offspring**
- **Cryopreservation of a testicular biopsy before starting treatment, followed by growing spermatogonial stem cells in the laboratoy and subsequent auto-transplantation is the only possibility for preservation of fertility in pre-pubertal boys**
- **Other experimental technological approaches to tackle infertility include testis tissue grafting, production of spermatozoa from SSCs in the lab & producing SSC from 'master' stem cells**

Struijk, BioMed Research International. 2012

Imperial College London

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
- If treatment required, options to be considered (and perhaps dismissed) include
  - Pheresis
  - Interferon
  - Tyrosine kinase inhibitors, avoid if possible
  - Hydroxycarbamide, avoid if possible

Milojkovic et al, Blood 2013

Imperial College London

CML diagnosed in pregnancy

Diagnosis of CML in pregnancy

1st Trimester

Leucapheresis
(Frequency to be determined by need to maintain WCC <100 x10^9/l and plts <500 x10^9/l throughout)

2nd Trimester

Leucapheresis
Consider IFNα

3rd Trimester

Leucapheresis
Consider IFNα

Milojkovic et al, Blood 2013

Imperial College
London

And it works!!!

Imperial College London

Management of fertility in women

- **Females are born with all the eggs (oocytes) they will ever have**
- **Begin to lose eggs from puberty during menstrual cycles**
- **Menopause when <1000 eggs remain: usually around 51 years in developed nations**

Imperial College London

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

Imperial College London

Imatinib in Pregnancy

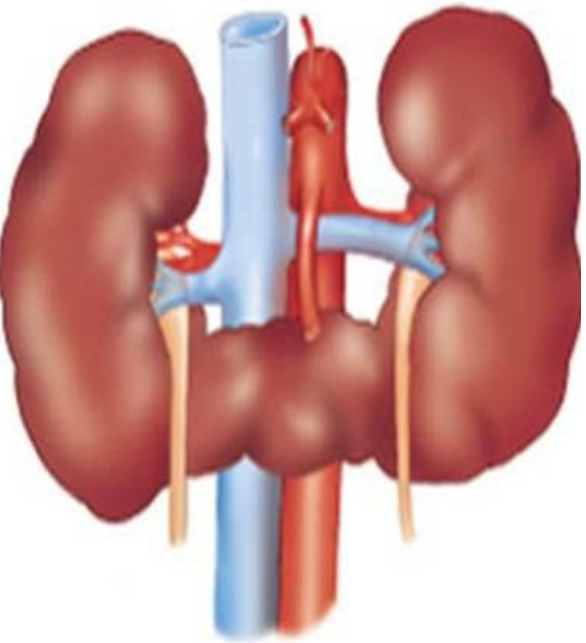
180 pregnancies reported on imatinib

- **We know the outcome of 125: 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**

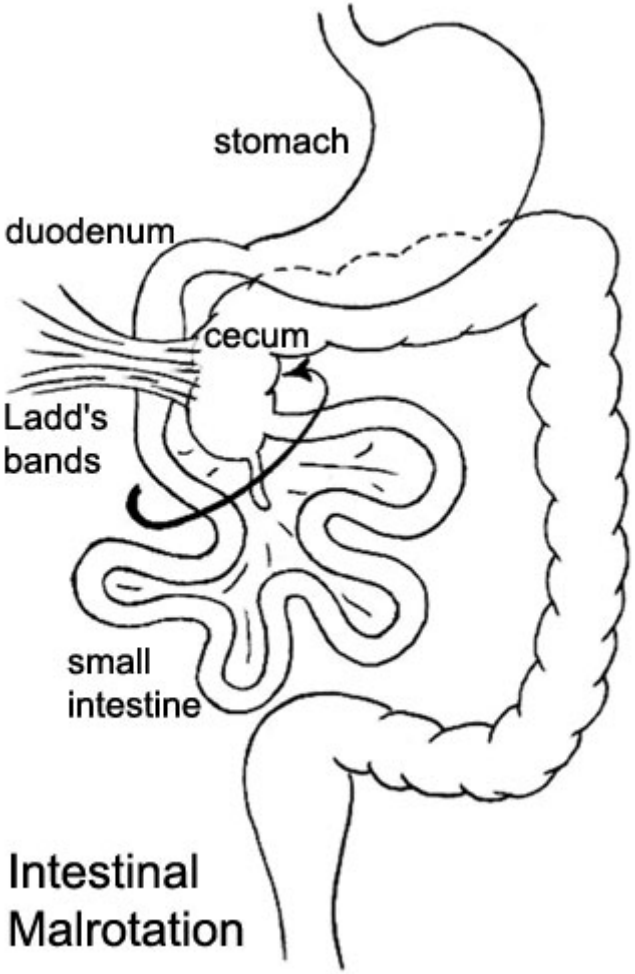
Pye et al. Blood. 2008; 111(12): 5505-5508.

Imperial College London

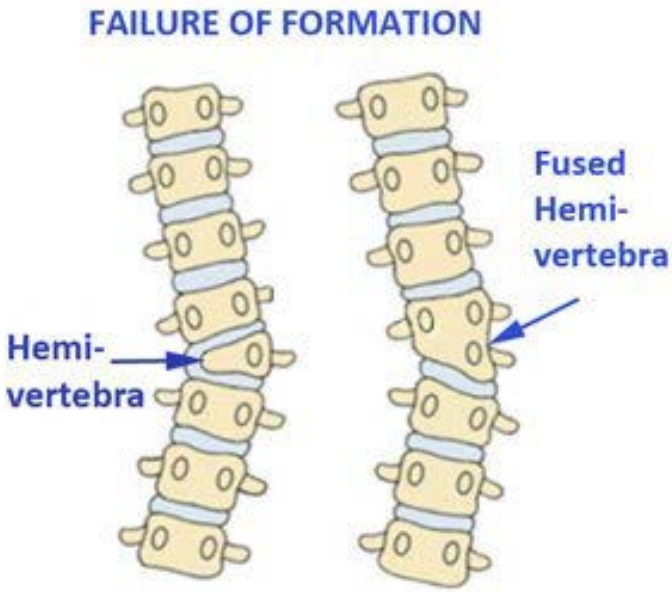
Examples of congenital malformations



Horsehoe kidney



Intestinal Malrotation



Imperial College London

Dasatinib and fertility in animal models

- **Pregnant rats were treated with 2.5-5mg/kg/day from 6-15 GD**
- **Death of pups with abnormalities of skeleton and kidneys**

- **Pregnant rats were treated from GD16, GD21 or onset of lactation**
- **Pups unlikely to survive even when dasatinib stated after organogenesis. Many developed pleural effusion**

- **Similar effects reported for nilotinib, bosutinib and ponatinib**

Imperial College London

Dasatinib in Pregnancy

78 pregnancies reported on dasatinib:

- **We know the outcome of 46 (59%): most stopped in first trimester**
  - **20/46 (43%) live births; 15 (33%) normal term infants**
  - **26/46 (59%) abortions; 18 (39%) elective and 8 (17%) spontaneous**
  - **7/46 (15%) congenital abnormalities; 2 identified at birth and 5 after elective termination**

Cortes et al, Am J Hematol 2015.

Imperial College London

Congenital Abnormalities on Dasatinib

Problem	Infant born at?	Infant outcome	Duration of dasatnib
Renal tract abnormalities	36 wks	Live-birth	Stopped at wk 4
Hydrops fetalis	28 weeks	Live-birth, died at 24 hrs	Given wks 17-24
CNS & skeletal abnormalities	NA	Elective termination	Stopped at wk 5
Hydrops fetalis	NA	Elective termination	Given wks 6-16

Congenital abnormalities (n=7, 2 at birth, 2 at SA, 3 at EA): details of remaining infants not available.

Cortes et al, Am J Hematol 2015.

Imperial College London

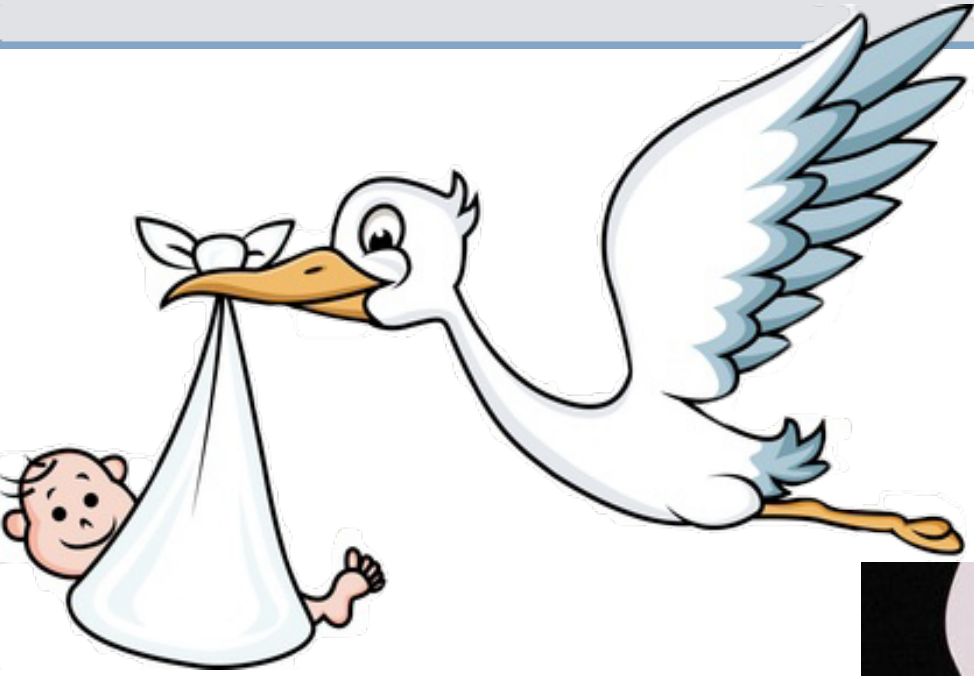
Nilotinib in pregnancy

Pregnancy Outcome after Nilotinib	N= 50
Abnormal pregnancies (SPC)	3/45(7%)
Omphalocele (TOP)	1
Transposition of vessels (IUD)	1
Heart murmur	1

Expert Rev Hematol. 2016 Aug;9(8):781-91

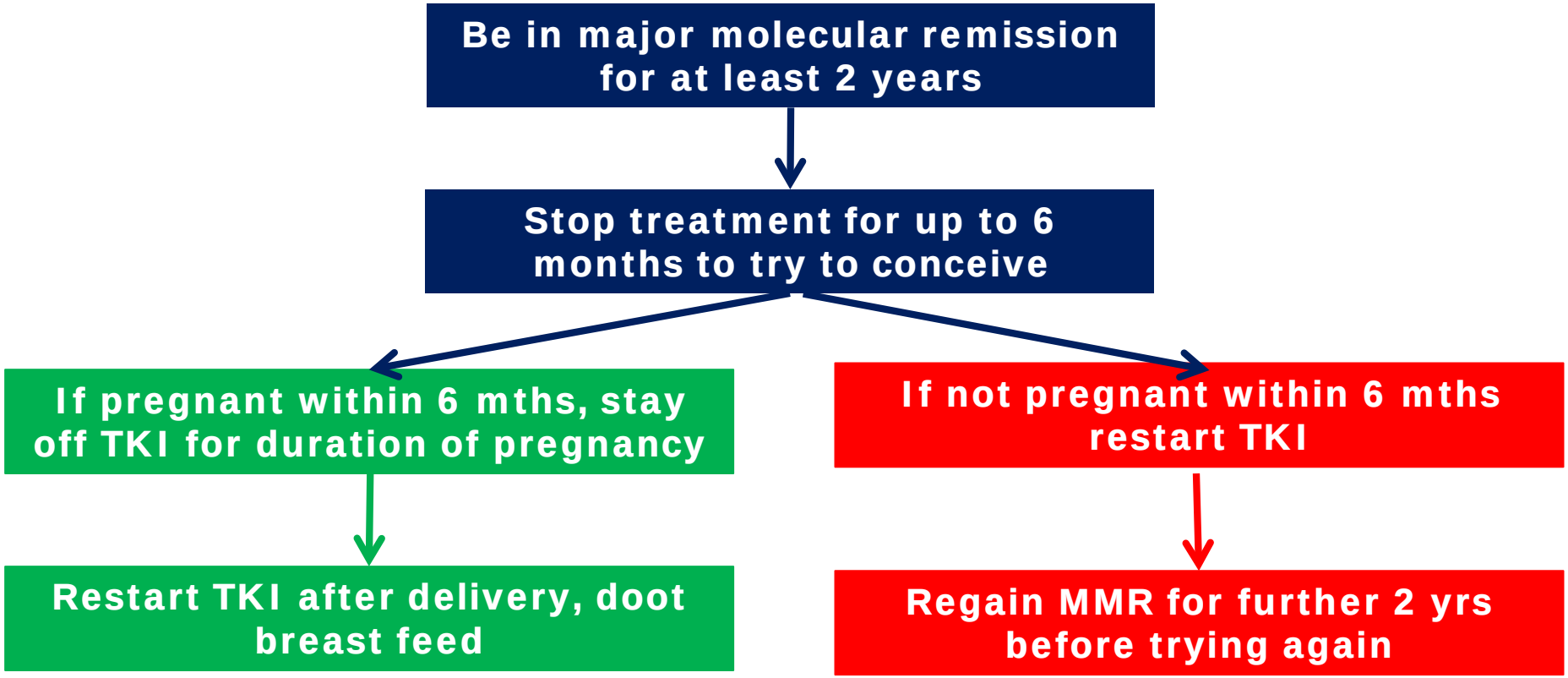
Imperial College London

Family planning in CML



Imperial College London

Advice for women who wish to become pregnant



Imperial College London

Advice for women who wish to become pregnant

Be in major molecular remission for at least 2 years

How should this be achieved?

Using a second generation TKI from diagnosis?

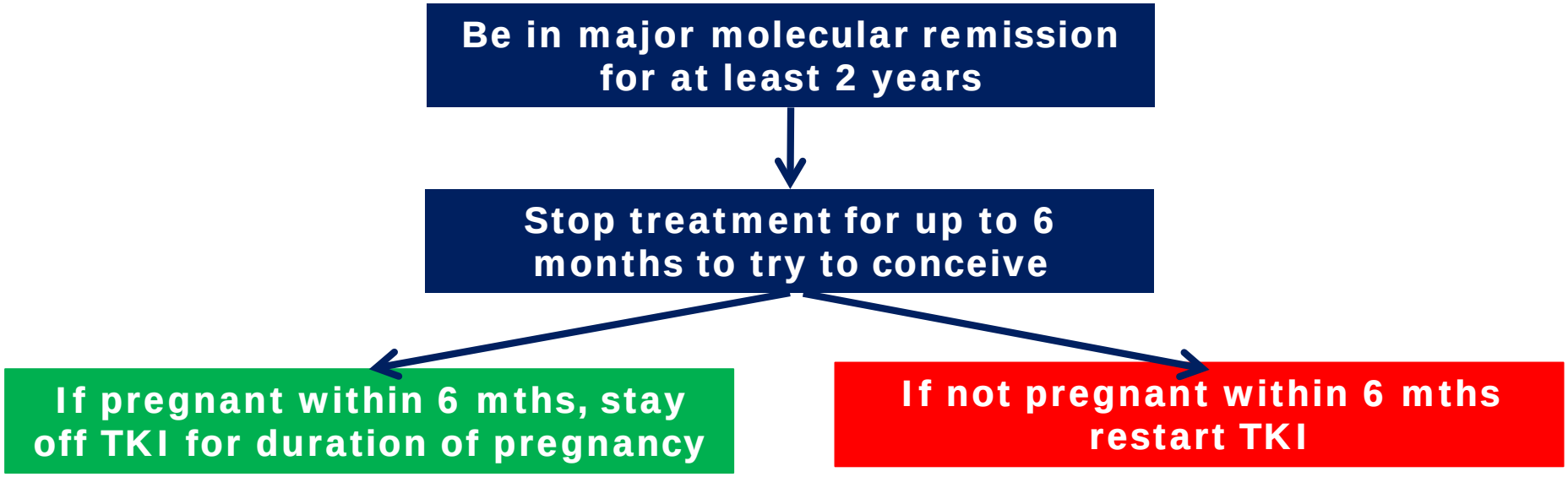
Changing to a second generation TKI if MMR not achieved by 12 mths?

Why not MR4 or MR4.5 or MR5?

What if MMR is not achieved but time is running out? Think about IVF or stop TKI for 2 weeks every month around ovulation. Restart after negative pregnancy test

Imperial College London

Advice for women who wish to become pregnant

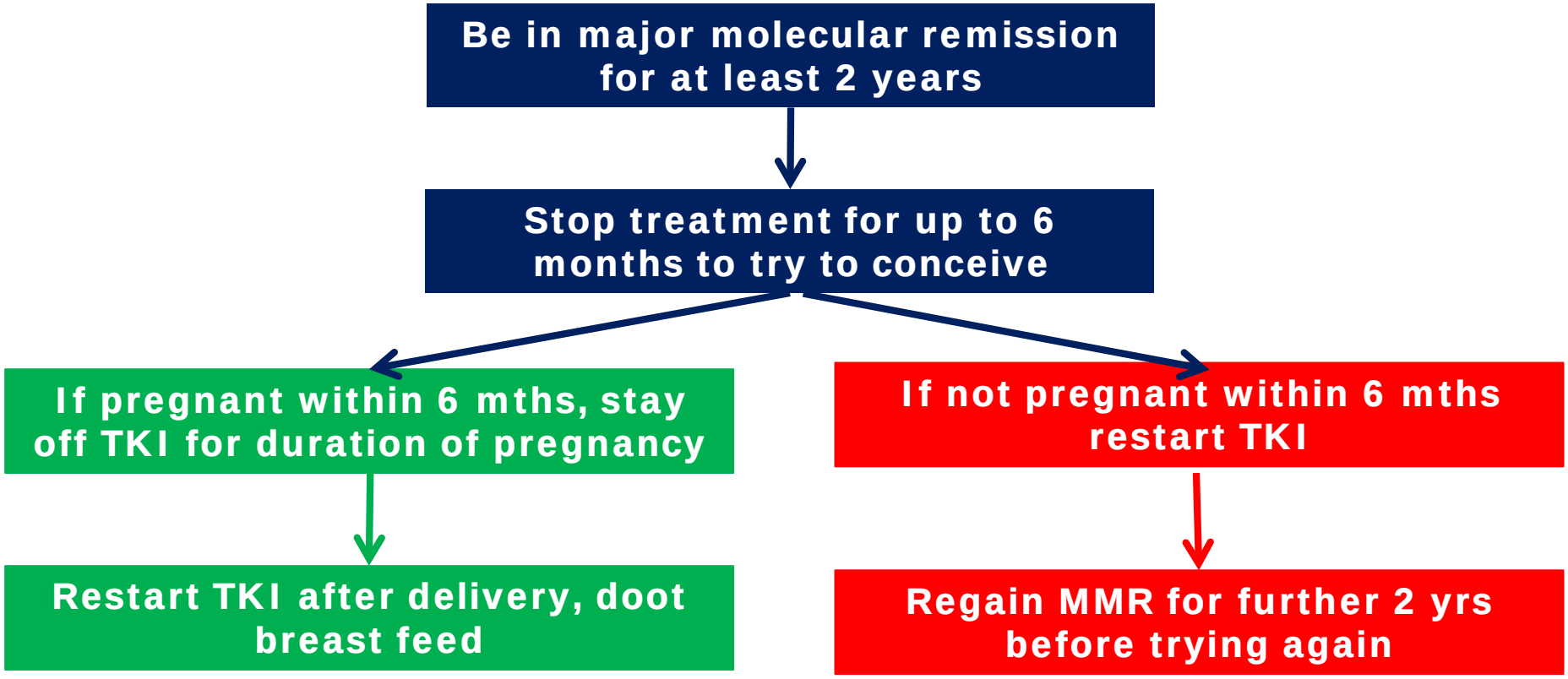


But stopping studies suggest up to 50% can remain off TKI indefinitely, so why insist on re-starting if PCR remains low?

If the patient has to restart for a rising PCR, which drug should be used?

Imperial College London

Advice for women who wish to become pregnant

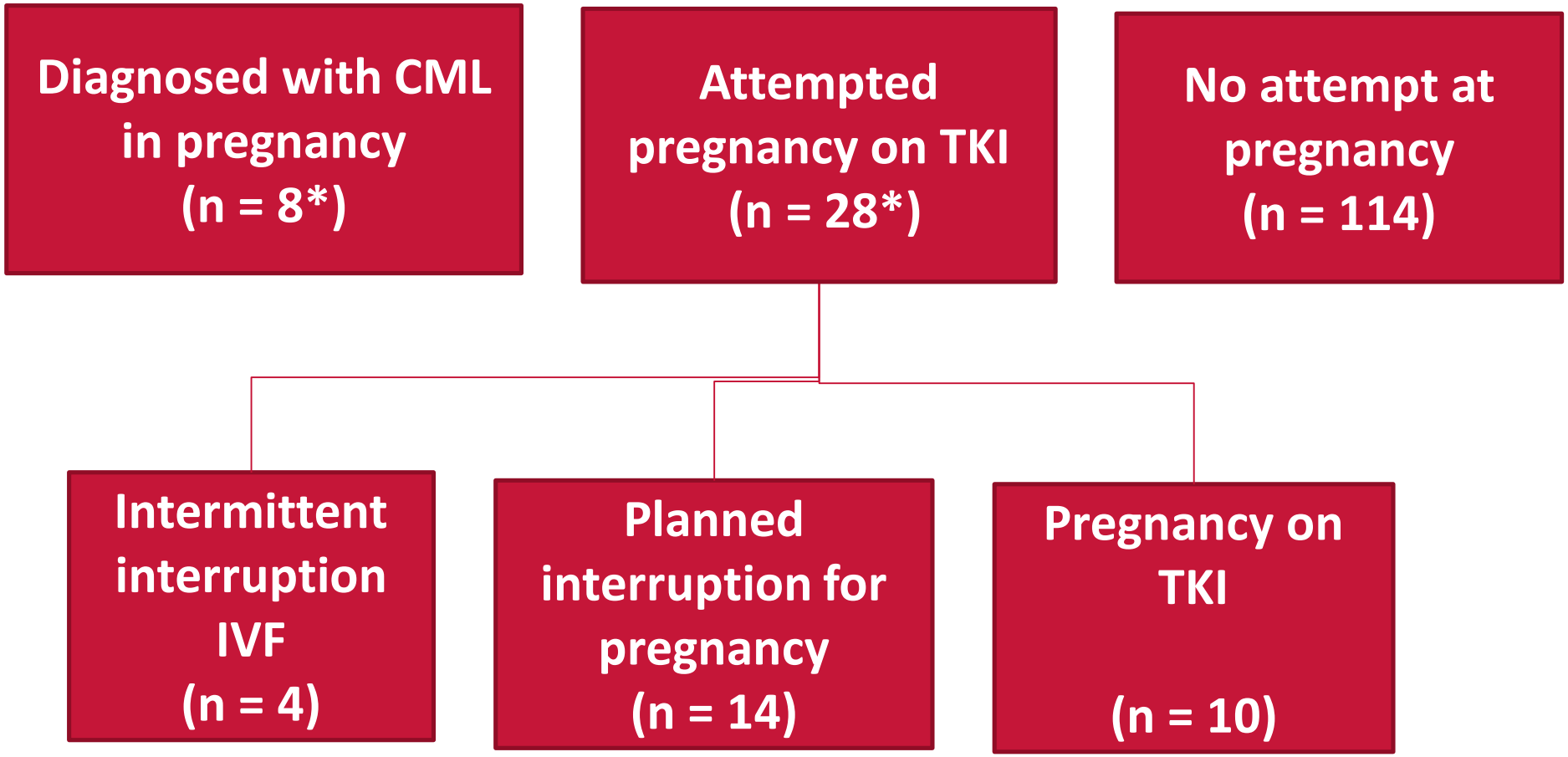


Does it have to be 2 years if you use a more potent drug?

If relapse was rapid, should there be another attempt?

Imperial College London

Parenting attempts in young female patients (n=174)



Courtesy of Louis Caldwell

Imperial College London

Disease outcomes for all interruptions

Response at stopping	n	MR3 lost	CCyR lost	CHR lost	MR3 regained	Baseline MR regained
MR2	6	-	5	2	-	5
MR3	8	7 (87.5%)	6	1	6 (86%)	6
MR4	11	5 (45.5%)	4	0	5 (100%)	5
MR4.5/5	10	7 (70%)	7	1	6* (60%)	5*
total	35	19 (72.5%)	22	4	17(90%)	21

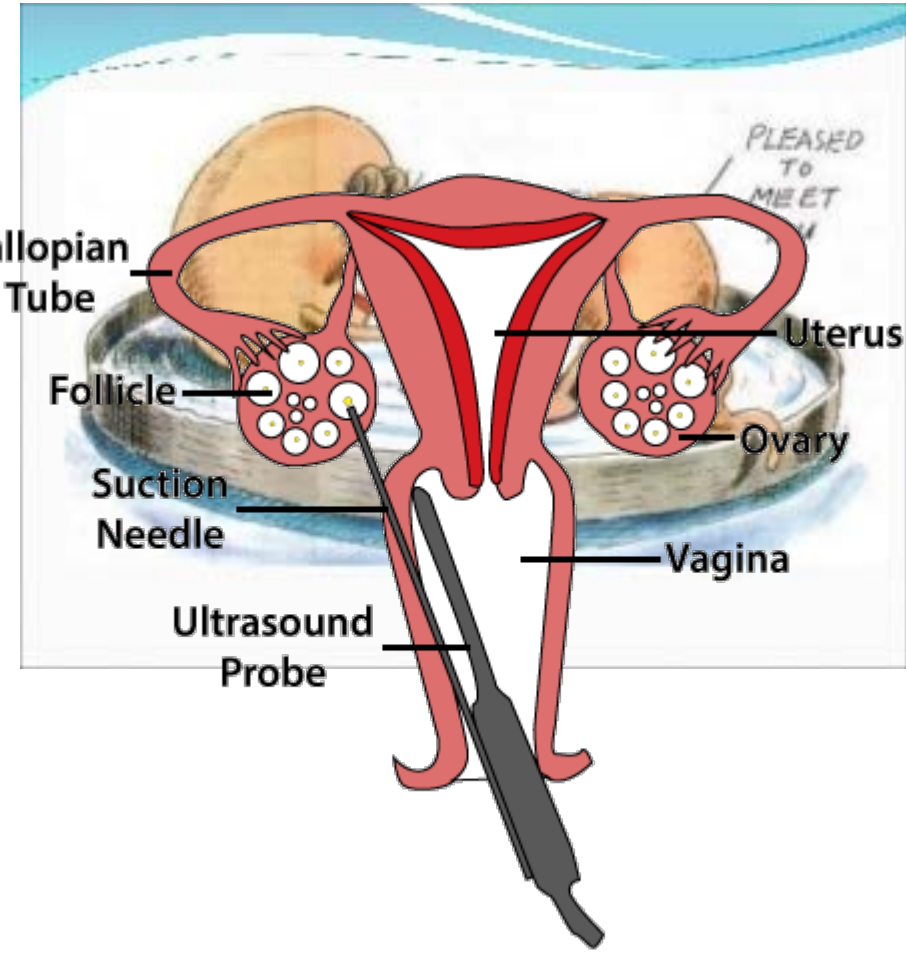
- **3 patients did not lose MR4.5 at any stage and remain off treatment**
- **1 patient has only just restarted TKI**

Courtesy of Louis Caldwell

Imperial College London

Reproductive options in women

- Natural childbirth
- IVF and embryo cryopreservation (25-30% success rate)
- Donor eggs and surrogacy
- Oocyte cryopreservation (>1000 babies now)



Imperial College London

Chance of pregnancy from fresh or frozen eggs

	Age of woman at time of egg collection				
	<35	35-37	38-40	41-42	>42
Fresh autologous	36%	33%	25%	16%	6%
Fresh donated	55%				
Thawed autologous	41%	33%	26%	23%	13%
Thawed donated	37%				

Cil et al, 2013

Imperial College
London

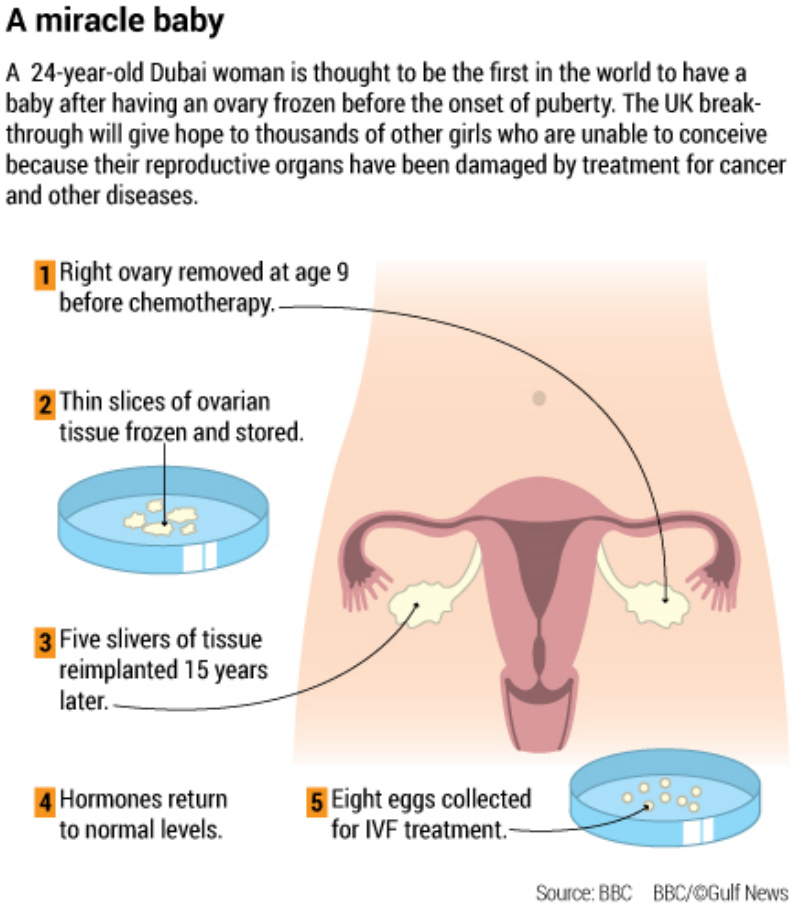
Young women

Imperial College London

Management of fertility in young women

Removal of ovarian tissue, re-grafted at a later date

- More than 35 live births to date
- 20 women were retransplanted with frozen ovarian tissue after cancer treatment. Ovarian activity resumed in all but one patient. 7 patients conceived, with 1 miscarriage & 4 ongoing pregnancies. 4 patients delivered healthy babies.



Biasin et al, BMT 2015, Dittrich et al, Fertility and Sterility 2015

Imperial College London

Elizabetta Abruzzese, Irene Caballes, Louise Caldwell, Simone Claudiani, Letizia Foroni, John Goldman, Stuart Lavery, Carolyn Millar, Dragana Milojkovic, George Nesr, Georgios Nteliopoulos, Renuka Palanicawander, Richard Szydlo, colleagues from Ariad, Bristol Myers Squibb, Incyte, Novartis and Pfizer