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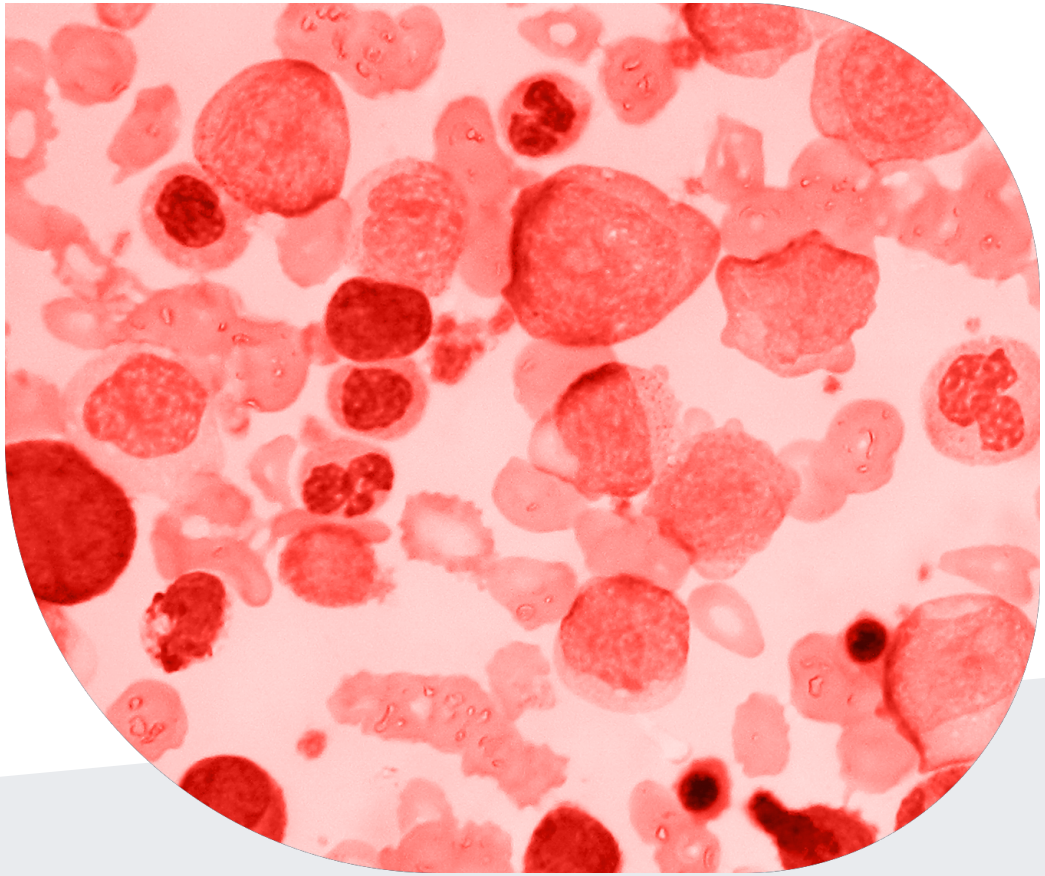
# CML: Pregnancy and Family Planning



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Edited by Dr Elisabetta Abruzzese

# Learning objectives

- Following review of these slides the reader should understand:
  - The challenges of fertility and pregnancy in CML patients
  - The three different gestation scenarios occurring in women with CML
  - What guidelines say regarding managing pregnancy in CML patients
  - The characteristics of different TKIs during pregnancy and breast feeding

CML, chronic myeloid leukaemia; TKI, tyrosine kinase inhibitor

# CML and pregnancy: the issue

- While CML is primarily a disease of later in life (~60 years) a good proportion of patients (~25%) are diagnosed ≤49 years of age[1] meaning that many CML patients are of reproductive age
- CML treatment goals have evolved from symptom and disease control to achieving high rates of deep remission and treatment cessation[2,3]
  - Most patients with chronic phase CML have normal life expectancies[3]
- With potential to achieve 'functional cure', focus has shifted to improving patient quality of life, including the ability to have children[4]
  - Annual incidence of pregnancies involving CML patients are 1/100,000 pregnancies[5]
- Management of CML in pregnancy is challenging due to the need to balance disease control in the mother against potential teratogenic effects of therapy on the foetus

CML, chronic myeloid leukaemia

[1] Hoglund M, et al. Ann Hematol 2015, Suppl2:S241–7; [2] Abruzzese E, et al. Eur J Haematol 2019;102:197–9; [3] Hochhaus A. Leukemia 2020:34;966–84; [4] Abruzzese E, et al. Ther Adv Hematol 2020;11:1–13; [5] Milojkovic D & Apperley JF. Blood 2014; 123:974–84.

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# Overview of TKIs and pregnancy I

| Drug | Preclinical data | Crossing placenta | Congenital abnormalities documented | Can TKI be introduced cautiously during pregnancy ? | Is TKI found in breast milk? |
|---|---|---|---|---|---|
| **Imatinib** | Some rat studies show reduced spermatogenesis and litter size,[1] while others show no spermatogenesis effect[2]<br>Female rats showed no fertility effects, although some experienced post implantation loss (foetal resorption & still births)[3] | Appears to cross placenta poorly.[4] Imatinib highly bound to plasma proteins and has high molecular weight limiting placental transfer[4] | Congenital abnormalities mostly observed when used during organogenesis, with common abnormalities including exencephaly, encephalopathies and abnormalities of skull bones[5] | In theory imatinib can be introduced after 15 weeks (point of placental maturation and critical organ formation) because of limited placental transfer but is not recommended by the manufacturer[6] | Imatinib has not been demonstrated to reach therapeutic concentrations in the infant's blood during breast feeding[7] |
| **Dasatinib** | Toxicities in rabbits and rats included skeletal malformations and embryolethality[8] | Placenta transfer of dasatinib observed[9] | Of three women treated with dasatinib during pregnancy, one normal infant and two with hydrops fetalis, one terminated and one delivered prematurely[10] | No[6] | Little published experience with dasatinib during breastfeeding. Alternate drugs may be preferred[11] |
| **Nilotinib** | Embryo-lethality and foetal effects (decreased foetal weight, visceral and skeletal variations) in rats and increased resorption of foetuses and skeletal variations in rabbits have occurred. In rats, maternal exposure to nilotinib caused reduced pup body weight with associated changes in physical development parameters[12] | Limited placenta transfer[13] | In the nilotinib investigator's brochure, 45 cases of drug exposure during pregnancy reported, with only one foetal abnormality[12] | Yes[6]<br>See imatinib | Nilotinib has not been demonstrated to reach therapeutic concentrations in the infant's blood during breast feeding[14] |

TKI, tyrosine kinase inhibitor

[1]Nurmio M, et al. Reprod Toxicol 2008;25:442–6; [2]Schultheis B, et al. Leuk Res 2012;36:271–4; [3]Gleevec PI. Available from: http://www.pharma..us.novartis.com/product/pi/pdf/gleevec_tabs.pdf, accessed October 2021; [4]Russel MA J Perinatol 2007;27:241–3; [5]Pye SM, et al. Blood 2008;111:5505-8; [6]Abruzzese E, et al. Ther Advances Haematol 2020;11:2040620720966120; [7]Gambacorti-Passerini CB, et al. Blood 2007;109:1790; [8]Dasatinib SmpC. Available from: https://www.ema.europa.eu/en/documents/product-information/sprycel-epar-product-information_en.pdf, accessed October 2021; [9]Berveiller P, et al. Anticancer drugs 2012;23:754-7; [10]Cortes JE, et al. Am J Hematol 2015;90:1111–5; [11]Dasatinib. Drugs and Lactation Database (LactMed) [Internet]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK500801, accessed October 2021; [12]Novartis SmPC. Available from: https://www.ema.europa.eu/en/documents/product-information/tasigna-epar-product-information_en.pdf, accessed October 2021; [13]Chelysheva E, et al. Leuk Lymphoma. 2018;59:733–8; [14]Chelysheva E, et al. Mediterr J Hematol Infect Dis 2018;10:e2018027.

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# Overview of TKIs and pregnancy II

| Drug | Preclinical data | Crossing placenta | Congenital abnormalities documented | Can TKI be introduced cautiously during pregnancy ? | Is TKI found in breast milk? |
|---|---|---|---|---|---|
| **Bosutinib** | Male rats: fertility slightly decreased. Female rats: increased embryonic resorption, decreases in implantation and viable embryos. Female rabbits: when administered during organogenesis foetal abnormalities included fused sternebrae and visceral abnormalities and decreased foetal body weight[1] | Evidence bosutinib crosses placenta in rats resulting in foetal exposure[1] | No specific bosutinib-induced abnormalities observed for 16 pregnant women treated[2] | No[1] | A study of $14^{C}$ radiolabelled bosutinib in rats demonstrated breast milk excretion[1] |
| **Ponatinib** | In rats, post-implantation loss, reduced foetal body weight, and multiple soft tissue and skeletal alterations have been observed at maternal toxic dosages.<br>Multiple foetal soft tissue and skeletal alterations were also observed at maternal nontoxic dosages<br>In rats female fertility parameters were reduced at dose levels corresponding to human clinical exposures. Evidence for pre- and post-implantation loss of embryos was reported in female rats and ponatinib may therefore impair female fertility[3] | Not known | Two pregnancies have been reported. One resulted in spontaneous abortion at 9 weeks and second a normal delivery[4] | No | Not known. Because ponatinib is more than 99% bound to plasma protein amount in breast milk likely to be low[5] |

TKI, tyrosine kinase inhibitor

[1]Bosutinib SmPC. Available from: https://www.ema.europa.eu/en/documents/product-information/bosulif-epar-product-information_en.pdf, accessed October 2021 [2]Cortes JE, et al. Int J Hematol Oncol 2020; 9:IJH26; [3]Ponatinib SmPC. Available from: https://www.ema.europa.eu/en/documents/product-information/iclusig-epar-product-information_en.pdf, accessed October 2021; [4]Abruzzese E, Personal Communication; [5]Ponatinib. Drugs and Lactation Database (LactMed) [Internet]. https://www.ncbi.nlm.nih.gov/books/NBK500859/, accessed October 2021.

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# Guidelines: CML and pregnancy I

| | European Leukemia NET[1] | National Cancer Center Network[2] | British Society of Haematology[3] |
|---|---|---|---|
| **Men** | Men planning fatherhood do not need to discontinue imatinib or 2GTKIs | TKI therapy does not have to be discontinued if pregnancy planned | The risks to partners of men taking imatinib or dasatinib are similar to the risks in the unaffected population. For remaining TKIs advise male patients considering parenting that there is a degree of uncertainty |
| **Women: TKI treatment** | TKI should be discontinued in 1st trimester as soon as pregnancy confirmed | Use of TKI (particularly in 1st trimester) should be avoided | It is reasonable to avoid TKIs throughout pregnancy |
| **CML drugs used in pregnancy** | Acetyl salicyclic acid and/or LMWH indicated for thrombocytosis. Leukapheresis and/or INFα are safe throughout gestation. Although imatinib has been used safely in 2nd and 3rd trimesters, insufficient experience does not allow routine use | INFα can induce and maintain haematologic remission. Recommends against use of hydroxyurea (especially in 3rd trimester). Leukapheresis, low dose aspirin and LMWH can be considered | If treatment required options include: leukapheresis, interferon and TKIs. Leukapheresis has least risk to foetus, INFα considered safe in later stages pregnancy |

2G, second generation; CML, chronic myeloid leukaemia; INFα, interferon alpha; LMWH, low molecular weight heparin; TKI, tyrosine kinase inhibitor

[1]Hochhaus A, et al. Leukemia 2020;34:996–84; [2]Deininger MW J Natl Compr Can Netw 2020:18;1385–415; [3]Smith G, Br J Haematol 2020;191:171–93.

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# Guidelines: CML and pregnancy II

| | European Leukemia NET[1] | National Cancer Center Network[2] | British Society of Haematology[3] |
|---|---|---|---|
| **Planned pregnancy** | Women eligible for trial of TFR can safely discontinue TKI to conceive. Women who lose MMR and not yet pregnant should restart treatment and discontinue when DMR re-established and maintained<br>Possible solutions include substitution of TKI with INFα or referral for alternative methods of conception | TKI should be stopped before attempting a natural pregnancy or oocyte retrieval, but optimum time of discontinuation unknown | Women with CML wishing to conceive should not have had previous TKI resistance and ideally have maintained MR[4] for ≥ 12 months before discontinuation<br>Patients in stable MMR for 1–2 years may be able to complete pregnancy without need for therapy |
| **Presenting during pregnancy** | N/A | N/A | Termination should not be advised unless at patient's request. If treatment required, options include leukapheresis, interferon and TKI |
| **Unplanned pregnancy** | N/A | Prompt consideration of holding TKI if therapy occurs while on imatinib, nilotinib, or dasatinib | Treatment should be discontinued immediately and foetal scans performed |

CML, chronic myeloid leukaemia; DMR, deep molecular response; INFα, interferon alpha; MMR, major molecular response; MR, molecular response; N/A, not available; TFR, treatment-free remission; TKI, tyrosine kinase inhibitor;

[1]Hochhaus A, et al. Leukemia 2020;34:996–84; [2]Deininger MW J Natl Compr Can Netw 2020:18;1385–415; [3]Smith G, Br J Haematol 2020;191:171–93.

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# Guidelines: CML and pregnancy III

| | European Leukemia NET[1] | National Cancer Center Network[2] | British Society of Haematology[3] |
|---|---|---|---|
| **Breast feeding** | Low level secretion of TKI in breast milk contraindicates use during breast feeding | Women on TKI should be advised not to breast feed as TKIs pass into human milk. In first 2–5 days after labour may be acceptable to avoid TKI to give child colostrum | TKIs are secreted in breast milk and breast feeding should be avoided while on treatment |
| **Monitoring** | Regular foetal ultrasound exams recommended | Monthly monitoring with qPCR. Recommended to Initiate treatment if BCR-ABL increases to >1.0% | N/A |
| **Fertility preservation** | N/A | Should be discussed with all patients of child bearing age before starting TKI therapy | N/A |

CML, chronic myeloid leukaemia; N/A, not available; qPCR, quantitative polymerase chain reaction; TKI, tyrosine kinase inhibitor;

[1]Hochhaus A, et al. Leukemia 2020;34:996–84; [2]Deininger MW J Natl Compr Can Netw 2020:18;1385–415; [3]Smith G, Br J Haematol 2020;191:171–93.

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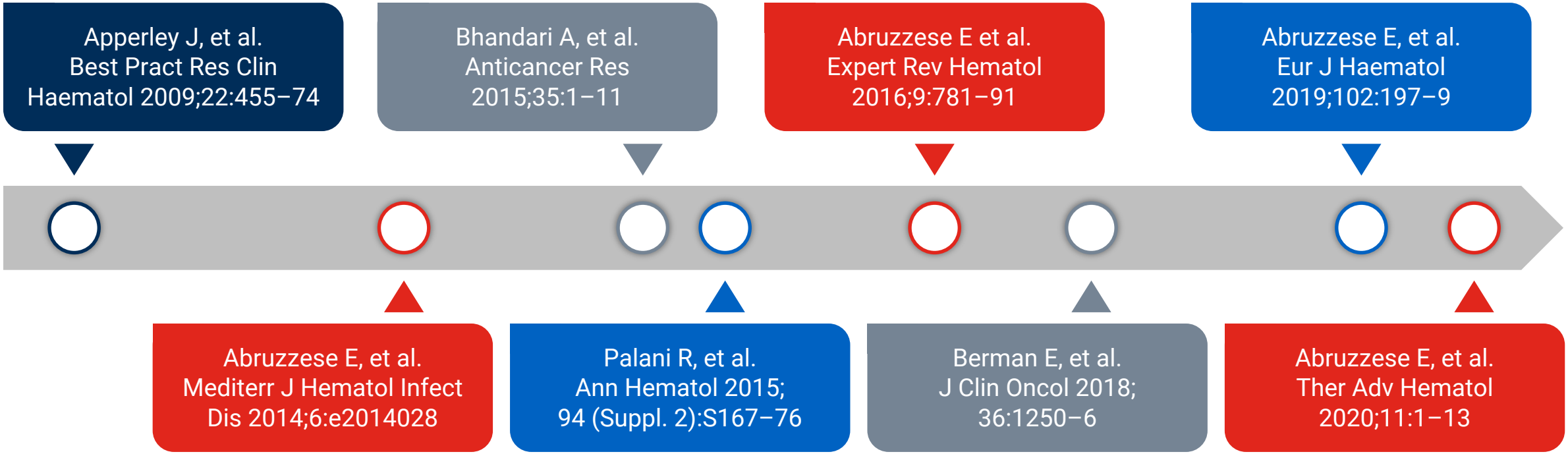
# Evolution of expert recommendations

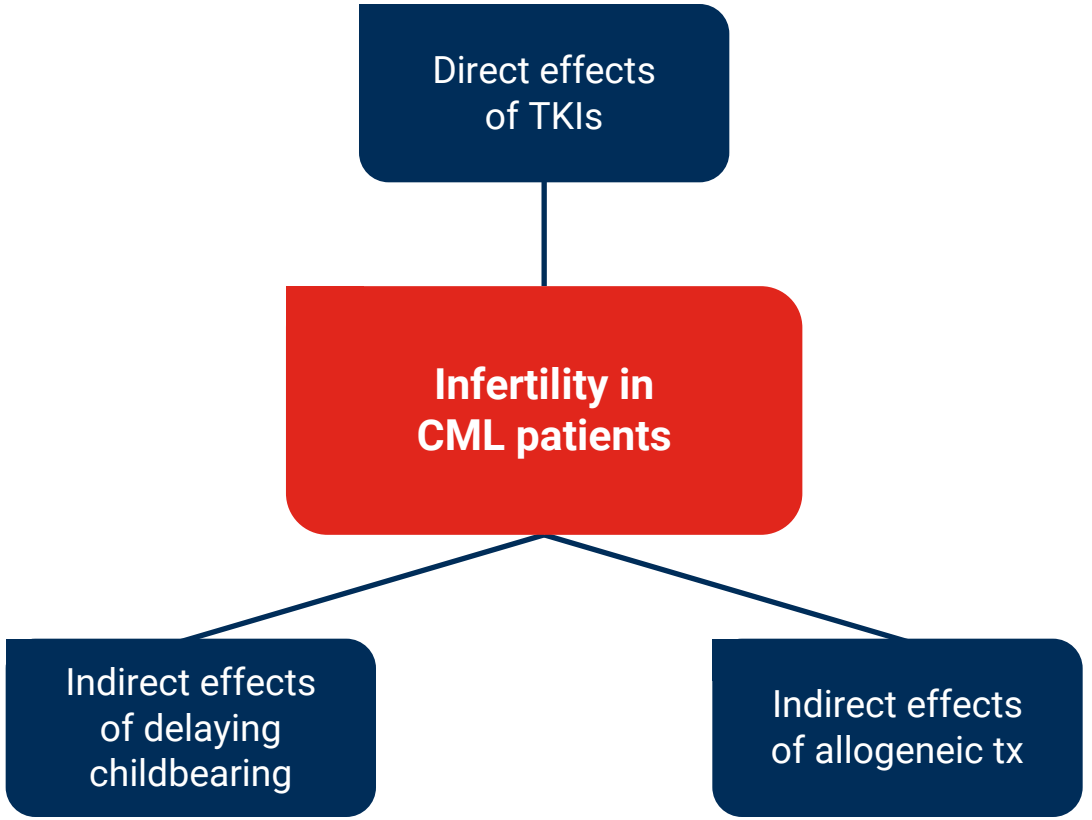
- With a lack of guidelines regarding management of fertility and pregnancy in CML patients a number of expert recommendations have been published which can be used for treatment guidance




CML, chronic myeloid leukaemia

# CML treatment and fertility

- Theoretically, BCR-ABL-targeting TKIs may affect fertility in males and females since they also have off-target effects on other tyrosine kinases (PDGFR, C-kit, Src) affecting gonadal development, and embryonic implantation[1,2]
- There have been few published reports on the effects of imatinib on human male fertility, with the exception of 2 case reports showing impaired spermatogenesis.[3,4] Additionally, studies have shown imatinib exposure leads to significant declines in testosterone levels in men with CML[5, 6]
- Clearly, women taking imatinib retain at least some level of fertility, evidenced by numerous reports of women conceiving while on therapy
- There are no published reports available for the fertility effects of other TKIs (dasatinib, nilotinib, bosutinib, ponatinib)




CML, chronic myeloid leukaemia; PDGFR, platelet-derived growth factor receptor; TKI, tyrosine kinase inhibitor; tx, treatment

[1]Milojkoviv D & Apperley J. Curr Opin Oncol 2008;20:112–21; [2]Nurmio M, et al. Reprod Toxicol 2008;25:442–6; [3]Seshadri T, et al. N Engl J Med 2004;351:2134–5; [4]Mariani S, et al. Fertil Steril 2011;95:1120.e15-e17; [5]Ghalaut VS. J Oncol Pharm Pract 2014;20:243–8; [6]Gambacorti-Passerini C, et al. Lancet 2003;361:1954–6.

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# Risks to conception with TKIs

## Men

- A systematic review of 428 pregnancies from 374 fathers not discontinuing TKI treatment before conception found malformations affected on average 2.5% of live births, which is comparable with the rate and also the type of malformations in the general population[1]
- For male patients trying to conceive there appear to be no limitations on use the use of TKIs since studies have not demonstrated genotoxicity of the drug or impaired fertility. If men are concerned there are options regarding sperm banking

## Women

- Based on published data, 10–20% of maternal exposure to TKIs during the first trimester ends in foetal problems or spontaneous abortion. The problems consist mainly of skeletal malformations, soft tissue abnormalities (especially involving vessel and organ formation) and small-for-date babies[2]
- In women, exposure to TKIs after conception may result in drug-related serious foetal malformations and higher risk of spontaneous abortion. Women should use contraception and if they become pregnant stop TKI treatment[3]
- To avoid babies being exposed to TKIs women can undergo oocyte retrieval before starting treatment with the embryos being cryopreserved until they come off treatment[4]

TKI, tyrosine kinase inhibitor

[1]Szakács Z, et al. PLoS ONE 15:e0243045; [2]Abruzzese E, et al. Mediterr J Haematol Infect Dis 2014;6:e2014028; [3]Abruzzese E, et al. Expert Rev Hematol 2016;9:781–91; [4]Abruzzese E, et al. Ther Adv Hematol 2020;11:1–13.

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# CML and treatment during gestation

**CML discovered during pregnancy**

Occasionally CML is found when routine blood investigations are performed during pregnancy[1]

CML does not alter the course of pregnancy, or pregnancy the course of CML[2]

**Pregnancy discovered during CML treatment**

If a patient becomes pregnant during TKI treatment she should immediately stop therapy[3]

The type of TKI used is important with the risk of complications being low for nilotinib and high for dasatinib[3]

**Planned pregnancy after stable disease response**

Treatment interruption for conception may be reasonable in women who have achieved DMR that would be considered eligible for treatment interruption[4]

Relapsing patients will most likely pass through the critical organ formation period not needing TKI treatment; while for non-relapsing patients the entire pregnancy and post partum breast feeding period can be TKI free[4]

CML, chronic myeloid leukaemia; DMR, deep molecular response; TKI, tyrosine kinase inhibitor

[1]Apperley J. J Natl Compr Canc Netw 2009:9:1050–8; [2]Sheehy WT. Am J Obstet Gynecol 1958;75:788–94; [3]Abruzzese E. et al Exp Rev Hematol 2016;9:781–91; [4]Abruzzese E, et al. Eur J Haematol 2019;102:197–9.

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# Gestation: CML discovered during pregnancy

- When CML is diagnosed in chronic phase, the WBC, platelets and weeks of gestation need to be taken into consideration
  - No action is needed for WBC 100,000–150,000 and platelets 500,000–1,000,000 (except aspirin)
  - Above these numbers leukapheresis and INFα can be considered throughout pregnancy[1]
  - If leukapheresis and INFα fail to control haematologic parameters, nilotinib, imatinib and hydroxyurea can be carefully evaluated but should only be used after week 16 when placenta has matured and organs formed[2]
  - Dasatinib should never be used during pregnancy due to high placental transfer rates and foetal effects (including hydrops fetalis)[3]
- When TKIs are given, response expectations in pregnant women mirror those in the non pregnant state (MR evaluation after 3 and 6 months recommended)[4]
- Prenatal testing is recommended following age and risk-related guidelines[4]
- After delivery women diagnosed during pregnancy should be treated according to established guidelines[4]
- For pregnant women presenting with CML in accelerated phase or blast crisis, the risk to the mother in delaying treatment is higher. Women are generally advised to terminate pregnancy to commence TKI therapy, unless the pregnancy is close to term[5]

CML, chronic myeloid leukaemia; INFα, interferon alpha; MR, molecular response; TKI, tyrosine kinase inhibitor; WBC, white blood count

[1]Abruzzese E, et al. Exp Rev Hematol 2016;9:781–91; [2]Abruzzese E, et al Clin Lymphoma, Myeloma and Leuk 2021;22 (Suppl 1):s153-5; [3]Cortes JE Am J Hematol 2015;90:1111–5; [4]Abruzzese E, et al. Ther Adv Haematol 2020;11:1–13; [5]Palani R et al Ann Hematol 2015;94 (Suppl 2):S167–76.

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# Gestation: pregnancy discovered during TKI treatment for CML

- Balancing the potential teratogenic risk to the foetus from TKIs against the risk to the mother of discontinuing treatment is difficult.
- Patients need to be educated about potential risks, particularly regarding first trimester exposure to TKIs and risk of relapse if treatment discontinued.
- In unplanned pregnancy, the TKI should be stopped as soon as pregnancy is suspected

## Pregnancy early in CML treatment <3 years[1]

- Residual leukaemia burden and response to therapy need to be taken into consideration
- For patients with high residual disease burden (≤MR[2]) resulting from short TKI exposure (<3–6 months) or longer exposure and suboptimal response, cases should be managed in a similar way to CML diagnosed during pregnancy (see previous slide)
- Patients in MMR at time of pregnancy with short TKI exposure present a substantial risk MR loss, with the option of INF, imatinib or nilotinib if BCR-ABL levels rise above 1–10% after 15–16 weeks

## Pregnancy late in CML treatment >3 years, not TFR eligible[1]

- Consideration should be given to replacing TKIs with IFN in first trimester, and additional consideration for use of imatinib or nilotinib in the later stages
- Avoid dasatinib

## Pregnancy late in CML treatment >3 years, TFR eligible[1]

- Patients who have been in DMR (MR[4] or better) for >12–24 months can be managed exactly as a patient eligible for a trial of discontinuation (see next slide)

CML, chronic myeloid leukaemia; DMR, deep molecular response; INF, interferon; MMR, major molecular response; MR, molecular response; TFR, treatment-free remission; TKI, tyrosine kinase inhibitor;

[1]Abruzzese E, et al. Ther Adv Hematol 2020;11:1–13.

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# Gestation: Planned pregnancy after stabilisation of CML response

- For women undergoing CML treatment who want to become pregnant there are no clear data on when safe to stop therapy. 'The Stop Therapy' trials required women to have at least MR[4] and most used MR[4.5] for at least 2 years. However, EURO-SKI[1] suggested patients with deep molecular response (BCR-ABL <0.01%) had same recurrence rate as those with MR[4.5]
- Recent expert recommendations suggest women have 2 years of sustained molecular negativity before attempting conception,[2,3,4] However, the reality is that most female CML patients will not meet standard criteria for stopping treatment during time frame of fertility
- To avoid contact with drug residues in tissue it is recommended women stop therapy at ovulation and restart if the menstrual cycle occurs[2]
- Large database analyses have reported safe discontinuation at first positive pregnancy test (between 3–5 weeks) since organ formation has not started and teratogenetic risk is very low[5]
- Patients coming off therapy must be informed about risk of relapse and monitored regularly with qRT-PCR[3]
- The majority of patients who lose response do so within 6 months of cessation, but typically regain MMR within several months of starting treatment[6,7]
- Ault et al found approx. 40% of women in haematologic remission at start pregnancy relapsed with interruption of imatinib therapy.[8] Patients were restarted on imatinib after 15 weeks gestation if BCR-ABL levels >1% and kept on observation if lower[9]
- Alternative options are brief cessation of treatment to allow for egg retrieval for use at a later time, or use of surrogate

CML, chronic myeloid leukaemia; MMR, major molecular response; MR, molecular response; qRT-PCR, real-time, qualitative polymerase chain reaction

[1]Mahon FX, et al. Blood 2016;128:787; [2]Abruzzese E. Exp Rev Hematol 2016;9:781–91; [3]Berman E, et al. J Clin Oncol 2018;36:1250–6; [4]Bhandari A, et al. Anticancer Research 2015;35:1–11; [5]Abruzzese E, et al. Blood 2019;134 (Suppl 1):498; [6]Hochhaus A, et al Leukemia 2017;31:1525–31; [7]Mahon FX Lancet Oncol 2010;11:1029–35; [8]Ault P, et al J Clin Oncol 2006;24:1204–8; [9]Chelysheva E, et al. Blood 2015;126:5144.

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# Treatment options according to pregnancy stage[1]

| 1st Trimester | 2nd Trimester | 3rd Trimester |
|---|---|---|
| • Leukapheresis (determined by need to keep white cell count <100 x$10^9$/L and platelets <500 x$10^9$/L[1]<br>• Avoid hydroxycarbamide and TKIs during organogenesis;[1] IFNα/pegylated IFNα can be used if necessary[2]<br>• Avoid TKIs during organogenesis and until placenta formed[3] | • Leukapheresis[1]<br>• Aspirin +/- LMWH if platelets >500-1,000 x$10^9$/L[1]<br>• INFα or pegylated IFNα may be considered[2]<br>• Consideration of use of imatinib/ nilotinib after 15/16 weeks pregnancy if BCR-ABL levels rise >1–10%[3]<br>• Avoid dasatinib[3] | • Leukapheresis[1]<br>• Aspirin +/- LMWH if platelets >500 x$10^9$/L[1]<br>• INFα or pegylated IFNα may be considered[2]<br>• Consideration of use of imatinib/nilotinib after 15/16 weeks pregnancy if BCR-ABL levels rise >1–10%[3]<br>• Avoid dasatinib[3] |

IFNα, interferon alpha; LMWH, low molecular weight heparin; TKI, tyrosine kinase inhibitor

[1]Palani R, et al Ann Hematol 2015; 94 (Suppl 2):S167–S176; [2]Kanellopoulou. Obstet Gynecol Ther 2017;1:1–4; [3]Abruzzese E, et al. Ther Adv Hematol 2020;11:1–13.

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# Outcomes of TKIs + pregnancy from case series. I

| Study | Drug | No. Patients | Findings: Female Patients | Findings: Male Patients | Conclusions |
|---|---|---|---|---|---|
| **Ault P et al., 2006**[1] | Imatinib | 18 (10 females + 8 males) | 2 pregnancies ended in spontaneous abortion. Of women interrupting therapy 5/9 in CHR at time of treatment lost CHR and 6 ↑ Philadelphia + metaphase.<br>At median 18 months after resuming imatinib, 8 had cytogenetic response | 1 pregnancy ended in spontaneous abortion | There is no evidence short exposure to imatinib during conception and pregnancy negatively affects developing foetus |
| **Cortes JE et al., 2015**[2] | Dasatinib | Outcomes available for 46 women + 33 partners of treated men | 15 (33%) delivered normal infant, 18 (39%) elective termination, 8 (17%) elective or spontaneous abortion. 5 (11%) abnormal pregnancy, 7 reports of foetal/ infant abnormalities (encephalocele, renal tract abnormalities, and hydrops fetalis). | 30 (91%) normal births reported for infants fathered by dasatinib treated men, 2 spontaneous abortions, 1 infant with syndactyly | Outcomes for most pregnancies conceived by men treated with dasatinib normal; due to small number of cases further monitoring required.<br>Significant effects on pregnancy outcomes in women treated with dasatinib support recommendations women avoid becoming pregnant and be informed of foetal risks |
| **Mukhopadhyay A et al., 2015**[3] | Imatinib | 22 pregnancies: 9 accidental, 13 planned (advised to stop treatment 1 month prior conception and 3 months after) | Resulted in 15 children (1 hypospadias, 1 mild hypospadias), 3 spontaneous abortions, 4 elective abortions | N/A | Planned therapy during pregnancy may be encouraged.<br>Imatinib therapy in unplanned pregnancy can cause spontaneous abortion and/or congenital abnormality |
| **Pye SM et al., 2017**[4] | Imatinib | 180 women (outcomes accessible for 125 patients) | 50% delivered normal infants, 28% elective terminations (3 following identification abnormalities), and 14% miscarriage.<br>Of live births, abnormalities observed in 12 infants, 3 with similar complex malformations (exomphalos) | N/A | Although most pregnancies exposed to imatinib are likely to be successful, there is a risk exposure may result in serious foetal malformation |

CHR, complete haematologic response; TKI, tyrosine kinase inhibitor

[1]Ault P, et al. J Clin Oncol 2006;27:1204–8; [2]Cortes JE, et al. Am J Hematol 2015;90:1111–5; Mukhopadhyay A, et al. Ir J Med Sci 2015;184:183–8; [4]Pye SM, et al. Blood 2008;111:5505–8.

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# Outcomes of TKIs + pregnancy from case series. II

| Study | Drug | No. Patients | Findings: Female Patients | Findings: Male Patients | Conclusions |
|---|---|---|---|---|---|
| **Abruzzese et al., 2018**[1] | IFN/ Imatinib/ Nilotinib/ Dasatinib/ Bosutinib/ Ponatinib | 52 female patients and 83 male patients. 166 pregnancies in total: male 106, female 60 | The majority of pregnancies were planned. MAPs were reported in 5M and 3F<br>Pregnancies in all cases progressed normally. In female patients there were 2 pre-eclampsia, oligohydramnios, 1 abruption placenta.<br>8 babies were born pre term and 2 were small at birth with no further consequences. 70% were delivered spontaneously. | Two spontaneous conceptions occurred in 2 males after allogeneic transplant.<br>8 babies born pre term and one baby was small at birth – no further consequences | TKI therapy has allowed CML patients to pursue a normal life including planning/managing a family.<br>Males do not need to stop therapy to conceive.<br>In contrast females must cease therapy due to the teratogenic nature of TKIs. |
| **Madabhavi I et al., 2019**[2] | Imatinib | 104: 46 female, 58 male (6 from pre-imatinib era) | Of 46 female patients, 25 full-term pregnancies, 17 spontaneous abortions, 4 elective abortions.<br>Continuing imatinib to delivery (n=10): 7 normal full-term deliveries, 1 preterm delivery, 1 omphlocele, 1 craniocynostosis.<br>Discontinuing imatinib (n=9): 8 normal full-term deliveries, 2 requiring leukapheresis, 1 died. Of 9 patients discontinuing, 2 lost MMR during 3rd trimester | Outcomes uneventful for full-term pregnancies in female partners of 58 male patients | No special safety measures are relevant for men receiving TKIs.<br>For women, clear no standard of care for best treatment CML in case of pregnancy |
| **De Moura AC et al., 2019**[3] | Imatinib/ dasatinib | Among 203 female CML patients 10 unplanned pregnancies in 7 women. 5 received TKIs between week 6 and 21 | 4 premature births, no maternal adverse events, foetal malformations or death.<br>1 patient lost CCyR and 2 lost HR | N/A | Patients planning to conceive advised to achieve stable deep molecular response to avoid risk disease progression |

CCyR, complete cytogenic response; CML, chronic myeloid leukaemia; HR, haematological response; IFN, interferon; MAPs, medically assisted pregnancies; MMR, major molecular response; N/A, not available; TKI, tyrosine kinase inhibitor

[1]Abruzzese E, et al. Blood 2018; 132 (Suppl. 1):43; [2]Madabhavi I, et al. J Glob Oncol 2019;1–11. doi: 10.1200/JGO.18.00211; [3]De Moura AC, et al. Haematol Transfus Cell Ther 2019;41:125–8.

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# Outcomes of TKIs + pregnancy from case series. III

| Study | Drug | No. Patients | Findings: Female Patients | Findings: Male Patients | Conclusions |
|---|---|---|---|---|---|
| **Abruzzese E, et al., 2019[1]** | Imatinib/ nilotinib/ IFN/ HU | 224 female patients<br>In 47 patients CML diagnosed during pregnancy.<br>75 patients had 80 pregnancies in DMR.<br>90 patients had pregnancies even though ≤MR3 | Of the 47 patients 48 children were born (one set of twins). Three were preterm (35–37 weeks). No births defects were observed.<br>Of the 75 patients, 81 children were born (6 patients had 2 pregnancies, 1 had twins) with one baby born preterm (week 35). No births defects were observed.<br>Of 90 patients ≤MR3 2 babies were born with polydactyly and hypospadias (IFN treatment since 1st trimester), and 2 exhibited a non-closed foramen ovale (IM during 2nd–3rd trimester) which was considered unlikely to be related to treatment. | N/A | CML patients can plan a family, with several caveats:<br>• Treatment with IFN is confirmed safe<br>• In contrast TKIs should not be used during pregnancy<br>• Selected TKIs (IM and NIL) which have little placental transfer, can be started after organogenesis.<br>• Patients at onset can delay therapy without jeopardising the future CML outcome. |
| **Assi R et al., 2021[2]** | TKIs (inc nilotinib + dasatinib) | 51 pregnancies involving 37 CML patients (30 women + 7 men).<br>15 women newly diagnosed during pregnancy, 19 being treated for chronic phase CML | Of 15 women diagnosed in pregnancy (10 no therapy): 12 pregnancies resulted in 14 healthy babies, 2 miscarriages 1 elective termination<br>Of 19 women conceiving taking TKIs: 29 pregnancies (20 unplanned, 9 planned). For unplanned 13 healthy babies (1 hypospadias), 5 miscarriages, 3 elective abortions.<br>For 7 women with 9 planned pregnancies, 6 healthy babies, 2 miscarriages, 1 premature delivery<br>7 women lost responses during pregnancy, at end pregnancy 5 regained response after resuming TKI | All 7 men fathered 7 full-term healthy babies.<br>No men interrupted TKI to plan for pregnancy<br>3 men reported erectile dysfunction while on TKI | While women may lose response following treatment interruption, on resuming therapy nearly all regained response |

CCyR, complete cytogenetic response; CML, chronic myeloid leukaemia; DMR, deep molecular response; HR, haematological response; HU, hydroxyurea; IFN, interferon; IM, imatinib; MR, molecular response; N/A, not available; NIL, nilotinib; TKI, tyrosine kinase inhibitor

[1]Abruzzese E, et al. Blood 2019;134 (Suppl 1):498; [2]Assi R, et al. Leuk Lymphoma 2021;62:909–17

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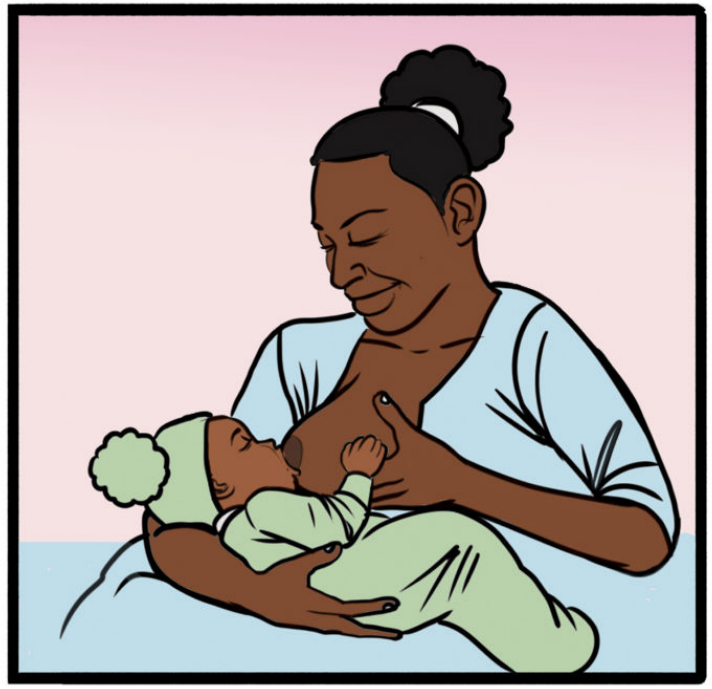
# Birth and breast feeding

- General anaesthesia as opposed to epidurals is the preferred option for CML patients undergoing caesareans due to potential risk of introducing blast cells into the CNS leading to development of CNS blast crisis[1]
- TKIs can be secreted into breast milk, so breastfeeding is not advised during therapy
  - A study with imatinib estimated that an exclusively breastfed baby would receive between 1.2 and 2 mg of the drug and metabolite daily with 400 mg/day maternal dose [2]
  - CML patients maintaining MMR after TKI discontinuation do not need to restart therapy after the baby is born and can safely breast feed[3]
  - All other CML patients can breast feed during the first 2–5 days after the birth before recommencing treatment to give the baby the benefit of colostrum.[4] Colostrum, the first form of milk produced by the mammary glands, contains a high amount of antibodies to protect new-borns against infections



CML, chronic myeloid leukaemia; CNS, central nervous system; MMR, major molecular response; TKI, tyrosine kinase inhibitor

[1]Datta R & Sharma A. Can J Anesth 2014;61:88–9; [2]Iqbal J et al. Leukemia & Lymphoma 2014;55:2109–13; [3]Abruzzese E, et al. Expert Review of Hematology 2016;9:781–91; [4]Abruzzese E. et al. Medit J Hemato infec Dis 2014; 6: e2014028.

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# Practical considerations

- Provide fertility/ pregnancy counselling at diagnosis for male and female patients who are fertile. Counselling should include risks to foetus of TKI exposure, options for fertility (fertility preservation and TKI treatment interruption)
- For successful management of CML pregnancy ensure good communication between haematologists, obstetricians and the neonatologists
- Prenatal testing is recommended following age and risk-related guidelines
- Patients coming off therapy must be informed about risk of relapse and monitored monthly with quantitative reverse transcriptase polymerase chain reaction (qRT-PCR)[1]
- Avoid breast feeding if on TKI

CML, chronic myeloid leukaemia; qRT-PCR, real-time, qualitative polymerase chain reaction; TKI, tyrosine kinase inhibitor

[1]Berman E et al. J Natl Compr Canc Netw 2018;16:660–2.

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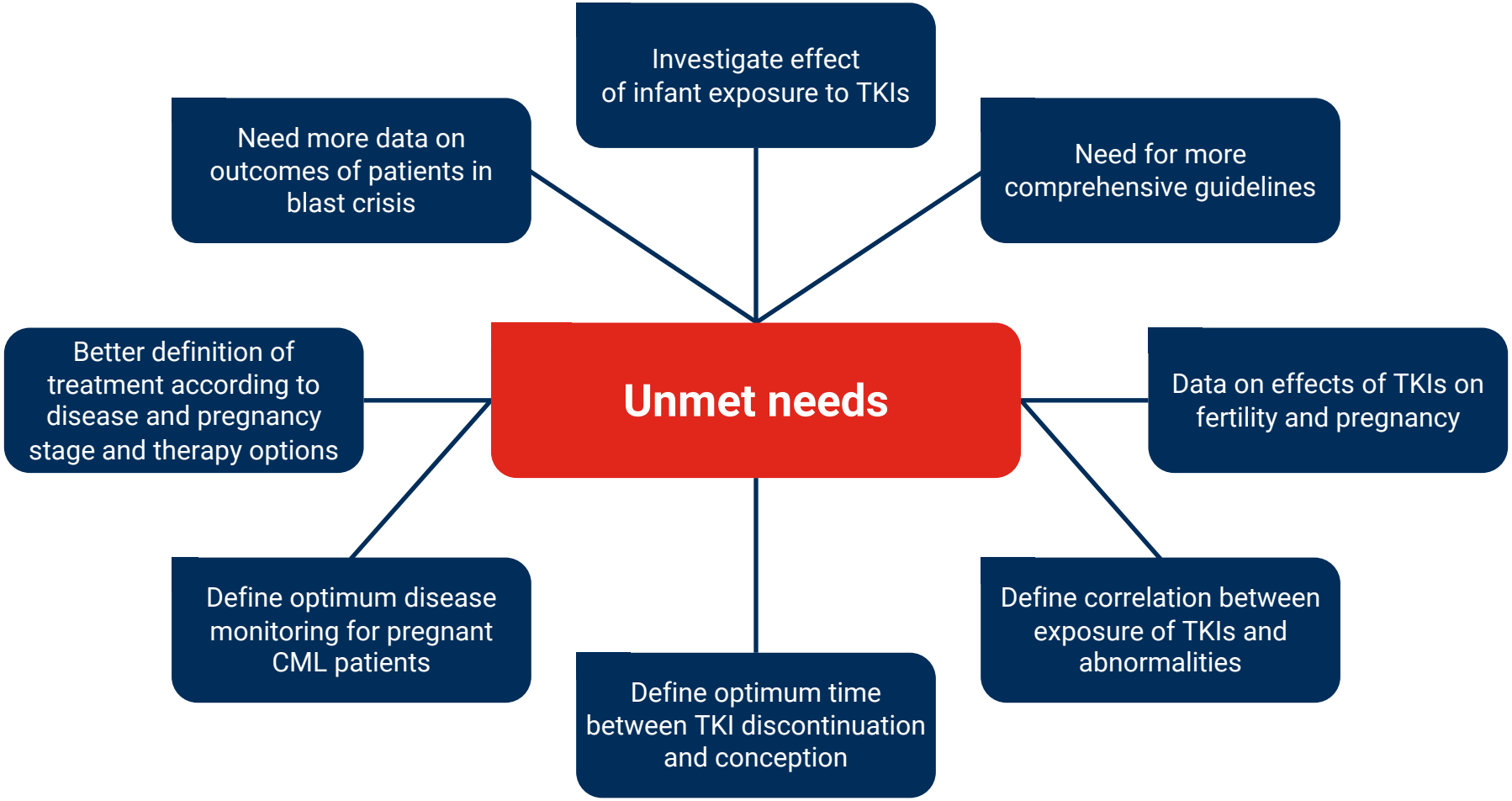
# Unmet clinical needs




CML, chronic myeloid leukaemia; TKI, tyrosine kinase inhibitor

# Conclusions

- Fertility issues should be discussed with CML patients at diagnosis
- For men with CML, there is no need to stop TKI treatment to father children
- For women with CML it has been demonstrated that TKI exposure after conception may result in serious foetal malformations and higher risk of spontaneous abortion
  - Treatment with TKI must be stopped at first pregnancy test and avoided during organogenesis
  - Ideally no TKI should be used during pregnancy. However, if TKIs are necessary imatinib and nilotinib are the preferred options as they do not seem to cross the placenta. Dasatinib should not be used at any time
- Other treatment options that can be considered during pregnancy include pegylated IFNα and leukapheresis
- More information is needed.
  - The national Italian (GIMEMA) and international (ELN) registries of conception/pregnancies in CML are ongoing in order to collect data and information regarding the most appropriate recommendations, counselling and outcome expectations

CML, chronic myeloid leukaemia; IFNα, interferon alpha; TKI, tyrosine kinase inhibitor

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