Special Feature

Issues of Imatinib and Pregnancy Outcome

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Abstract

The introduction of tyrosine kinase inhibitors into clinical practice now offers most patients with chronic myelogenous leukemia lengthy remissions and the possibility of normal life expectancies. These improved survivals have resulted in the need to address issues relating to quality of life, including fertility and procreation. Treatment may require lifelong daily therapy with drugs that might inhibit proteins essential to gonadal function, implantation, and embryogenesis. Animal data suggest that imatinib at standard dosages is unlikely to impair fertility in either adult male or female animals. However, human data remain limited, particularly in children and adolescents. Children born to men who are actively taking imatinib at conception seem healthy, and current advice is not to discontinue treatment. In contrast, data are less encouraging for children born to women exposed to imatinib during pregnancy. Although numbers are small, a disturbing cluster of rare congenital malformations has prevented imatinib from being recommended safely, particularly during the period of organogenesis. Alternative strategies for managing pregnancy in chronic myelogenous leukemia include one or both of regular leukapheresis and interferon-α. Pregnancy in advanced-phase disease presents particular problems. (*JNCCN* 2009;7:1050–1058)

The use of tyrosine kinase inhibitors (TKIs) in the management of chronic myelogenous leukemia (CML) has changed the natural course of the disease to such an extent that considerations regarding quality of life have become almost as important as those of preservation of life. For many patients, one of the clearest indications of good quality of life is the ability to conceive children and raise a family. Physicians caring for patients with CML are not infrequently asked for advice regarding the need for, and/or the appropriateness of stopping, treatment in order to conceive.

For obvious reasons, data regarding safety of TKIs before, during, and after gestation remain limited. In this context, one must remember that Bcr-Abl is not the only target of the TKI; imatinib inhibits not only Abl but also c-kit, platelet-derived growth factor receptors α and β (PDGFR-α/β), ARG, and c-FMS. Dasatinib, a second-generation TKI, also inhibits Src and related proteins. Several of these proteins are known to have functions that may be important in gonadal development, implantation, and fetal development.[1–5] An international registry of pregnancy outcome was recently established by Novartis to compile pregnancy outcomes in women who have been exposed to imatinib and nilotinib, but some years may elapse before further data are available. In the meantime, any recommendations regarding the management of CML in pregnancy must take into consideration this lack of information.

Although most patients with CML experience prolonged remissions while taking a TKI, approximately 20% might require alternative therapies, including allogeneic stem cell transplantation.[6] Because identifying these individuals before treatment is impossible, future fertility must be considered at diagnosis in all patients of child-bearing age. Semen cryopreservation is recommended before start of treatment and women should be counseled on oocyte, ovarian, and embryo storage.

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Experience From Animal Models

Males

Animal studies investigating the effects of imatinib on gonadal function have yielded confusing results.[7] Lower testicular weights along with a reduction in the number of motile sperm were observed in male rats who received imatinib, 60 mg/kg, for 70 days (equivalent to the human dose of 600 mg/d).[7] This was not seen at doses of 20 mg/kg or less (equivalent to 200 mg/d). The fertility of male and female rats was not affected.

When immature male rats (aged 5–7 days) were exposed to these higher doses of imatinib for only 3 days, gonocyte migration, growth of the testis, formation of spermatogonial stem cell and Leydig cell pools, and proliferation of differentiating type A spermatogonia were all impaired.[8] Surprisingly, however, by the age of 11 weeks, the exposed animals had normal epididymal sperm counts, although gonadotrophins levels remained elevated above the normal range. The authors concluded that treatment with imatinib early in life caused a permanent reduction in testicular size and resulted in altered reproductive hormone levels, suggesting the presence of compensatory mechanisms designed to maintain normal testicular function. The investigators speculated that treatment with imatinib before puberty may have more deleterious effects than exposure in adulthood.

These data were later confirmed by Basciani et al.,[9] who administered intraperitoneal imatinib (50 mg/kg) to newborn male mice for 5 days and observed a profound reduction of spermatogonia, that returned to normal as the mice aged. These investigators ascribed the effects of imatinib to inhibition of PDGFR-β, which is known to be required for proliferation and migration of gonocytes in the early postnatal period. Nurmio et al.[10] later showed a reduction in litter size from adult male rats that had been treated with imatinib in early postnatal life compared with untreated littermates. Reassuringly, no differences were seen in the fertility index, live birth index, sex ratio, or frequency of survival to time of weaning.

In contrast, no differences in spermatogenesis were seen between imatinib-treated and untreated adult mice when they were exposed to imatinib, 150 mg daily, continuously for 2 months (Junia Melo, MD, PhD, and Roger Gosden, PhD, DSc, personal communication). Spermatogenesis was studied using the microscopy of the seminiferous tubules together with measurement of their diameter (an index of spermatogenic activity) and determination of the number of sperm. This suggests that intermediate-term treatment, at least in adult male mice, is not associated with impairment of gonadal function.

Females

Data are sparse relating to TKI effects on ovarian function. During the development of imatinib for clinical use, female rats were given imatinib 14 days before mating and through day 6 of gestation.[7] Fertility was not affected. Rats given doses of 45 mg/kg or more experienced postimplantation loss, evidenced through early fetal resorption or stillbirths, nonviable pups, and early pup mortality between postpartum days 0 and 4. If imatinib was administered during organogenesis at doses of 100 mg/kg or more, it induced teratogenic effects, including exencephaly or encephalocele, absent or reduced frontal bones, and absent parietal bones. At doses higher than 100 mg/kg, total fetal loss was noted in all animals. Fetal loss was not seen at doses of 30 mg/kg or less (approximately equivalent to 300 mg). In the first-generation offspring at this same dose level, mean body weights were reduced from birth until terminal sacrifice. First-generation offspring fertility was not affected.[7]

In the studies by Melo and Gosden, female mice were also given imatinib, 150 mg/kg, orally for 2 months (Junia Melo, MD, PhD, and Roger Gosden, PhD, DSc, personal communication). The ovaries were examined for morphologic differences and changes in the numbers of follicles at all stages of development (primordial, primary, secondary, tertiary). No differences were observed between imatinib-treated and control mice. In addition, there was no increase in follicular atresia in the animals exposed to the TKI, suggesting that there may be no effect on fertility.

Effects of Imatinib on Human Fertility

A recent publication described the development of oligospermia after exposure to imatinib,[11] and another reported the occurrence of primary ovarian failure in a 30-year-old woman within 2 years of starting imatinib.[12] Although these reports have not been substantiated, it would seem prudent to continue to

recommend strategies to preserve fertility from time of diagnosis. Adult male patients should be offered semen cryopreservation, but unfortunately boys diagnosed before the onset of puberty still cannot be provided a realistic hope of future parenting ability. Female patients of child-bearing age with stable partners may wish to consider embryo cryopreservation. Those without partners should be referred for discussion of ovarian and/or oocyte retrieval and storage.

Effects of Imatinib During Conception and Pregnancy

Men

Increasing evidence shows that children born to men who were taking imatinib at conception do not have an increased risk for congenital malformations. An early report from the Novartis group described 13 pregnancies in the partners of men who were taking imatinib at conception. The outcome was known for only 8 of these; 3 ended in abortion (2 therapeutic and 1 spontaneous), 1 in utero death occurred at 13 weeks, and 4 normal pregnancies resulted in 4 normal infants.[13]

A later report from M. D. Anderson was more encouraging, with 7 normal pregnancies and 1 spontaneous abortion in the partners of 8 men treated with imatinib for a median of 20 months. One infant was born with a malrotation of the gastrointestinal tract, which required surgical correction.[14] After these initial publications, another 10 uneventful pregnancies were reported in the partners of 9 men on both standard and high doses of imatinib.[15,16] More recently, Novartis reported awareness of more than 60 pregnancies in the partners of men treated with imatinib without any suggestion of an increased risk for pregnancy-associated complications or congenital abnormalities (Novartis personnel, personal communication).

Women

The literature describes several case reports of pregnancy outcome in women who conceived while taking imatinib but ceased treatment either in the first trimester or remained on drug throughout the pregnancy, with most reporting favorable outcomes.[17–32] Recently, full outcome data have been reported for 125 women from a total of 180 known to have conceived while on imatinib. These results have given considerable concern regarding drug safety (Table 1).[33] Most of these women (70%) were exposed to imatinib only during the first trimester, but 26% remained on treatment throughout their pregnancy (i.e., until elective or spontaneous abortion or birth).

Table 1 Outcome of Pregnancies Associated With the Use of Imatinib

Pregnancy Outcome	Number
Elective abortion (fetal abnormalities identified)	3
Elective abortion (fetal abnormalities unknown)	32
Spontaneous abortion	18
Still birth with fetal abnormalities	1
Live births with fetal abnormalities	8
Normal live births	63
Outcome unknown	55
Total	180

Data from Pye SM, Cortes J, Ault P, et al. The effects of imatinib on pregnancy outcome. Blood 2008;111:5505–5508.

Of the 125 pregnancies with known outcome, 63 resulted in the birth of normal live infants, with 18 of the women receiving imatinib throughout their pregnancy. Among these 125 pregnancies, 35 (28%) underwent elective terminations—3 after the identification of fetal abnormalities. The remaining fetuses were either not examined or had no defects identified. Furthermore, 18 pregnancies (14.4%) ended in spontaneous abortion, which is within the limits expected in the normal population (10%–15%). Among the remaining 9 infants, 8 live and 1 still births occurred, all with congenital abnormalities.

In total, 12 pregnancies resulted in infants with fetal abnormalities. The dose (but not exact duration) of imatinib taken by the mother was known for 10 of these cases, but the data were insufficient to assess any potential relationship between cumulative dosage and the occurrence of fetal abnormalities. No maternal exposure to alcohol, tobacco, or drug addiction during pregnancy was reported in any of these cases, and none of the mothers had undergone any high-dose chemotherapy before their pregnancies.

Table 2 provides additional details of the defects seen in the 9 infants born with abnormalities (3 fetuses were aborted because of identified abnormalities). Cases 2 through 4 (in Table 2) are notable because the combinations of defects were strikingly similar and because similar bony defects were ob-

served in rodent studies. The expected incidence of exomphalos in the general population is approximately 1 in 3000 to 4000 births,[34] and the finding of 3 cases of 180 is far higher than would be predicted. The most likely candidate whose inhibition might be responsible for the induction of these abnormalities is the tyrosine kinase receptor PDGFR-α. Mice homozygous for null mutations in PDGFR-α showed birth defects, including facial clefting, severe spina bifida occulta, cardiac defects, omphalocele, renal and urogenital anomalies, and vertebral and rib fusion abnormalities.[35,36] These data are derived from spontaneous reports and therefore subject to some potential reporting bias, but remain the most comprehensive set of data on the effect of imatinib in pregnancy. This information is sufficiently concerning for physicians to advise all female patients to avoid conception while taking imatinib.

Table 2 Congenital Abnormalities Described in Children Born to Women Who Conceived While Taking Imatinib

Case	Abnormalities
1	Premature closure of the skull sutures (craniosynostosis)
2	Hypoplastic lungs, exomphalos, duplex left kidney, absent right kidney, hemivertebrae, and a right shoulder anomaly
3	Exomphalos, right renal agenesis, and hemivertebrae
4	Exomphalos and scoliosis
5	Communicating hydrocephalus, cerebellar hypoplasia, and cardiac defects
6	Meningocele (stillborn)[22]
7	Hypospadias
8	Hypospadias
9	Pyloric stenosis[25]

Data from Pye SM, Cortes J, Ault P, et al. The effects of imatinib on pregnancy outcome. Blood 2008;111:5505–5508.

Effects of Imatinib Postpartum

It is not known whether imatinib mesylate or its metabolites are excreted in human milk. However, both were extensively excreted in the milk of female rats administered 100 mg/kg. The concentration in the milk was approximately 3-fold higher than in plasma. Estimates suggested that approximately 1.5% of a maternal dose would be excreted into milk, which is equivalent to a dose given to an infant of 30% of the maternal dose per unit body weight.

Subsequently, imatinib levels have been measured in the milk of women taking imatinib postpartum. Of the 3 reports, 2 have identified substantial excretion of imatinib into breast milk and in 1 patient the active metabolite *N*-DesM-IM accumulated approximately threefold in breast milk compared with plasma levels.[37–39] Because of the potential for serious adverse reactions in nursing infants, breast feeding should be strongly discouraged for women taking imatinib.

Managing Pregnancy in CML

Two distinct scenarios exist regarding pregnancy and CML. The first is when the pregnancy antedates the CML diagnosis, wherein it is discovered when the patient undergoes the blood tests associated with managing the pregnancy, usually in the early part of the second trimester. The second is when pregnancy occurs, planned or unplanned, after CML is diagnosed and treatment was already initiated. Clearly, the situations have important similarities, particularly with respect to the subsequent management, because therapies other than TKIs may be necessary for disease control until delivery.

Diagnosis During an Established Pregnancy

The occurrence of CML in women of child-bearing age is rare, but diagnosis during pregnancy is common. Disease detection is undoubtedly an opportunistic observation and occurs at this time because the blood counts performed in early pregnancy are the first such measurements in that woman's recent lifetime. This diagnosis adds considerable complexity to management, because fear of risk to the infant, and loss of happiness usually associated with pregnancy, adds to the patient's trauma from being diagnosed with a potentially fatal disease.

For pregnant patients with CML in chronic phase, treatment is probably unnecessary if the white cell count remains below 100 x 10^9/L and the platelet count is less than 500 x 10^9/L, but this is not confirmed. Therapies other than TKIs include interferon-α (IFN-α), hydroxyurea, busulphan, and leukapheresis, although hydroxyurea and busulphan should be avoided if treatment is required in pregnancy (Table 3). Busulphan is an alkylating agent that

Table 3 Reported Effects on Fertility and Embryonic Development of Chemotherapy Commonly Used in CML

Drug	Reported Effects	Reference
Busulphan	Teratogenic in animal models, has been associated with birth defects in humans	39,40
Hydroxyurea	Fetal growth retardation, fetal death, and an increased incidence of congenital anomalies including craniofacial, limb, and trunk defects	41–45
Interferon-α	Nonteratogenic in rats and rabbits, resulting in normal offspring but has abortifacient effects in rhesus monkeys at doses of 90 and 180 times the recommended dose of 2×10^6 IU/m^2	57–61

does not alter the natural course of the disease and is inferior to both hydroxyurea and IFN-α in terms of overall and progression-free survival. It is now rarely used in the management of CML in chronic phase and should certainly be avoided in pregnancy.[40,41]

Case reports of 5 women with a history of CML, treated with hydroxyurea at conception, all of whom continued the drug during pregnancy, show that 4 delivered normal infants. The remaining woman developed eclampsia at 26 weeks gestation and a morphologically normal male infant was subsequently delivered stillborn.[42–45] Overall, the risk for teratogenicity does not seem as high as suggested by animal models, but again avoiding this drug in pregnancy seems prudent unless no alternative exists. Hydroxyurea is known to be excreted in breast milk and therefore should not be given to lactating women.[46]

Regular leukapheresis may avoid drug therapy and be particularly useful during the first trimester of pregnancy.[47–51] Occasionally the platelet count may not be adequately controlled using leukapheresis alone and aspirin or low molecular weight heparin (LMWH) may be required. The safety profile of these agents in pregnancy has been investigated at some length and has reassuring results.[52–57] For women requiring additional treatment during pregnancy, either because of intolerance to leukapheresis or poorly controlled counts, IFN-α may have a role in the second and third trimesters. Several case reports exist of successful pregnancies in women receiving IFN-α at all stages of pregnancy and for various conditions, including CML.[58–61] Because of its large size (19,300 da), IFN-α probably does not cross the placental barrier significantly.[62] Thus, the drug is probably safe in pregnancy, although avoiding its use if not essential would seem prudent. No data are available on the safety of IFN during breastfeeding, and whether any components of the drug are excreted in breast milk is unknown.

Pregnancy After Diagnosis and Initiation of Treatment

Unplanned Pregnancies While on Imatinib

In the case of an unplanned pregnancy while taking imatinib, balancing the risk to the fetus if the mother continues imatinib against the risk to the mother if she interrupts treatment remains difficult. From the fetal perspective, imatinib should be discontinued because of the potential risk for serious developmental abnormalities, but from the maternal perspective this may not be appropriate. Another option would be to continue imatinib and have the pregnancy closely monitored, with termination considered if any significant abnormalities are identified. In these circumstances, the couple should be made aware of potential risks, particularly regarding first trimester exposure. Considerations include the wishes of the parents, mother's disease status, current response to imatinib, availability of suitable alternative therapies, and ability to reinduce responses to imatinib after a prolonged period off-treatment.

Planned Pregnancies on Imatinib

The advice given to women who wish to become pregnant after the diagnosis and initial treatment of their disease will most probably differ according to the current response to treatment. Given the association of congenital abnormalities with first trimester exposure to imatinib, the drug should be discontinued before attempts to conceive. Controversy exists regarding the time that should elapse between cessation of treatment and unprotected intercourse, but advising women to wait a few days to permit the

washout of imatinib from the body seems reasonable.

For patients with optimal responses (i.e., in major or complete molecular remissions), this author believes patients can reasonably discontinue treatment to allow attempts at conception. Given that patients will not take imatinib for the duration of the pregnancy, physicians may consider suggesting that the period from stopping imatinib to becoming pregnant should not exceed 6 months. Patients who have experienced very large reductions in tumor load are unlikely to require any therapy until after delivery, although regular monitoring with reverse transcriptase polymerase chain reaction should be instigated. If the response to TKI is less good, then cessation may lead to cytogenetic or hematologic relapse.[63] A plan for managing these pregnancies is presented in Table 4.

Ault et al.[14] previously reported on 10 women who interrupted treatment with imatinib because of pregnancy. Of the 9 in complete hematologic response (CHR) when imatinib was stopped, 6 had an increase in Ph-positive metaphases and 5 lost their CHR while off treatment. At a median of 18 months after restarting imatinib, these 9 women were again in CHR, and although all experienced a cytogenetic response, it was complete in only 3. Although this might be considered a poor response, because the rate of complete cytogenetic response at 18 months in patients who receive uninterrupted imatinib from diagnosis is 75% to 90%, these 9 women showed improved response to treatment after pregnancy compared with prepregnancy results.

Rousselot et al.[64] recently showed that imatinib can be discontinued in some patients under certain favorable circumstances. Imatinib was discontinued in 12 patients who had all been in complete molecular remission for at least 2 years; 6 developed molecular relapse within 5 months of stopping imatinib therapy but the remaining 6 in complete molecular remission at a median follow-up of 18 months. Of those who experienced relapse, most achieved a complete molecular response again a short time after reintroduction of imatinib.

Pregnancy in Advanced-Phase Disease

Pregnancy in advanced-phase disease is usually unplanned and extremely difficult to manage. The relevant data are largely derived from patients who develop acute leukemia during pregnancy.[65] To give patients the best possible chance for remission (or, in the case of CML, a second chronic phase), treatment should be administered promptly and subsequent courses delivered in a timely manner. Most patients with advanced-phase disease will have previously been exposed to imatinib, and prolonged responses to a second-generation TKI are rarely durable. The alternative is to use combination chemotherapy akin to that used in acute myeloblastic or lymphoblastic

Table 4 Optimizing Management of Female Patients With CML Who Are Planning a Pregnancy

Preconception	Ideally 24 months in MMolR before discontinuing imatinib
	Counseling on risk to infant if imatinib continued and risk to mother if discontinued
	Limit attempts at conception to within a certain interval to prevent prolonged periods off-treatment
Imatinib washout	Unknown, but no more than 7 days
Disease monitoring	Blood counts monthly; real-time quantitative PCR 2–3 times monthly
	No treatment if CMolR/MMolR
	Consider treatment if loss of MMolR or CCyR
	Administer treatment if loss of CHR
	Leukapheresis in first trimester if treatment required
	Leukapheresis or IFN-α in second or third trimester if treatment required
Postdelivery	Restart imatinib, with urgency dependent on reverse transcriptase PCR results; if MMolR, breastfeeding could be permitted
	For all other disease status, restart imatinib and advise against breastfeeding

Abbreviations: CCyR, complete cytogenetic response; CHR, complete hematologic response; CML, chronic myelogenous leukemia; CMolR, complete molecular response; IFN-α, interferon-α; MMolR, major molecular response; PCR, polymerase chain reaction.

leukemia. If the pregnancy is in the first trimester at diagnosis, delaying treatment until after delivery is not an option because the mother or child is unlikely to survive to term.

Chemotherapy given during the first trimester for any malignancy confers the highest risk for congenital malformation, estimated from studies in acute leukemia to be between 10% to 23%. The possible impact of intensive chemotherapy on fetal development during the first trimester of pregnancy must be explained, and the mother must also realize what consequences delaying this treatment will have on her own health. In this situation, many women may elect termination.

Combination chemotherapy given during the second and third trimesters is widely accepted to be associated with fewer complications; in general, the later in the pregnancy chemotherapy is given, the fewer the risks to the fetus. However, caution should be exercised when administering chemotherapy near the time of delivery. Ideally, patients should recover from therapy-induced pancytopenia before delivery.

If the leukemia presents late in pregnancy, early delivery is strongly encouraged with intensive supportive therapy using blood products and growth factors and a delay in the administration of chemotherapy. If treatment is deemed essential, the attending obstetrician should be aware that the child may be born anaemic, neutropenic, or thrombocytopenic. Appropriate measures must be taken at delivery and the infant closely monitored, and then followed up after birth. The use of second-generation TKIs has not been described in this situation.

Summary

In one decade, TKIs have revolutionized the management of CML and radically changed the outlook for patients. CML has become a lifelong chronic ailment, the management of which must now adapt to, rather than dictate, the patient's lifestyle. For male patients, fathering children can be achieved without interruption of treatment. For female patients, particularly those with more advanced disease, management is more complicated. However, with counseling and a considered approach to disease monitoring, many women wishing to conceive can minimize risk to both mother and infant.

References

1. Soriano P. Abnormal kidney development and hematological disorders in PDGF beta-receptor mutant mice. Genes Dev 1994;8:1888–1896.
2. Soriano P. The PDGF alpha receptor is required for neural crest cell development and for normal patterning of the somites. Development 1997;124:2691–2700.
3. Hoch RV, Soriano P. Roles of PDGF in animal development. Development 2003;130:4769–4784.
4. Tybulewicz VL, Crawford CE, Jackson PK, et al. Neonatal lethality and lymphopenia in mice with a homozygous disruption of the c-abl proto-oncogene. Cell 1991;65:1153–1163.
5. Mauduit C, Hamamah S, Benahmed M. Stem cell factor/c-kit system in spermatogenesis. Hum Reprod Update 1999;5:535–545.
6. de Lavallade H, Apperley JF, Khorashad JS, et al. Imatinib for newly diagnosed patients with chronic myeloid leukemia: incidence of sustained responses in an intention-to-treat analysis. J Clin Oncol 2008;26:3358–3363.
7. Novartis Pharmaceuticals Corporation. Gleevec Full Prescribing Information. Updated, May 2009. East Hanover, New Jersey. Available at: http://www.pharma.us.novartis.com/product/pi/pdf/gleevec_tabs.pdf. Accessed November 4, 2009.
8. Nurmio M, Toppari J, Zaman F, et al. Inhibition of tyrosine kinases PDGFR and C-Kit by imatinib mesylate interferes with postnatal testicular development in the rat. Int J Androl 2007;30:366–376.
9. Basciani S, De Luca G, Dolci S, et al. Platelet-derived growth factor receptor beta-subtype regulates proliferation and migration of gonocytes. Endocrinology 2008;149:6226–6235.
10. Nurmio M, Kallio J, Toppari J, Jahnukainen K. Adult reproductive functions after early postnatal inhibition by imatinib of the two receptor tyrosine kinases, c-kit and PDGFR, in the rat testis. Reprod Toxicol 2008;25:442–446.
11. Seshadri T, Seymour JF, McArthur GA. Oligospermia in a patient receiving imatinib therapy for the hypereosinophilic syndrome. N Engl J Med 2004;351:2134–2135.
12. Christopoulos C, Dimakopoulou V, Rotas E. Primary ovarian insufficiency associated with imatinib therapy. N Engl J Med 2008;358:1079–1080.
13. Hensley ML, Ford JM. Imatinib treatment: specific issues related to safety, fertility, and pregnancy. Semin Hematol 2003;40(2 Suppl 3):21–25.
14. Ault P, Kantarjian H, O'Brien S, et al. Pregnancy among patients with chronic myeloid leukemia treated with imatinib. J Clin Oncol 2006;24:1204–1208.
15. Ramasamy K, Hayden J, Lim Z, et al. Successful pregnancies involving men with chronic myeloid leukaemia on imatinib therapy. Br J Haematol 2007;137:374–375.
16. Breccia M, Cannella L, Montefusco E, et al. Male patients with chronic myeloid leukemia treated with imatinib involved in healthy pregnancies: report of five cases. Leuk Res 2008;32:519–520.
17. Meera V, Jijina F, Shrikande M, et al. Twin pregnancy in a patient of chronic myeloid leukemia on imatinib therapy. Leuk Res 2008;32:1620–1622.
18. Buyukbayrak EE, Ergen B, Karsidag YK, et al. Pregnancy complicated with chronic myelogeneous leukemia (CML) successfully treated with imatinib: a case report. Arch Gynecol Obstet 2008;278:161–163.

19. Yilmaz M, Demirhan O, Kucukosmanoglu E, et al. Pregnancy in patients with chronic myeloid leukemia treated with imatinib. Leuk Lymphoma 2007;48:2454–2456.
20. Koh LP, Kanagalingam D. Pregnancies in patients with chronic myeloid leukemia in the era of imatinib. Int J Hematol 2006;84:459–462.
21. Ali R, Ozkalemkas F, Ozcelik T, et al. Pregnancy under treatment of imatinib and successful labor in a patient with chronic myelogenous leukemia (CML). Outcome of discontinuation of imatinib therapy after achieving a molecular remission. Leuk Res 2005;29:971–973.
22. Ali R, Ozkalemkas F, Ozkocaman V, et al. Successful pregnancy and delivery in a patient with chronic myelogenous leukemia (CML), and management of CML with leukapheresis during pregnancy: a case report and review of the literature. Jpn J Clin Oncol 2004;34:215–217.
23. Choudhary DR, Mishra P, Kumar R, et al. Pregnancy on imatinib: fatal outcome with meningocele. Ann Oncol 2006;17:178–179.
24. Prabhash K, Sastry PS, Biswas G, et al. Pregnancy outcome of two patients treated with imatinib. Ann Oncol 2005;16:1983–1984.
25. AlKindi S, Dennison D, Pathare A. Imatinib in pregnancy. Eur J Haematol 2005;74:535–537.
26. Heartin E, Walkinshaw S, Clark RE. Successful outcome of pregnancy in chronic myeloid leukaemia treated with imatinib. Leuk Lymphoma 2004;45:1307–1308.
27. Garderet L, Santacruz R, Barbu V, et al. Two successful pregnancies in a chronic myeloid leukemia patient treated with imatinib. Haematologica 2007;92:e9–10.
28. Suppiah R, Kalaycio M. Successful outcome of pregnancy in a patient with chronic myelogenous leukemia exposed to imatinib during the first trimester. Leuk Lymphoma 2006;47:1149–1150.
29. Skoumalova I, Vondrakova J, Rohon P, et al. Successful childbirth in a patient with chronic myelogenous leukemia treated with imatinib mesylate during early pregnancy. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub 2008;152:121–123.
30. Dolai TK, Bhargava R, Mahapatra M, et al. Is imatinib safe during pregnancy? Leuk Res 2009;33:572–573.
31. Sora F, De Matteis S, Bajer J, et al. Persistence of molecular remission throughout pregnancy in CML after imatinib. Leuk Res 2009;33:e6–e7.
32. Klamova H, Markova M, Moravcova J, et al. Response to treatment in women with chronic myeloid leukemia during pregnancy and after delivery. Leuk Res 2009;33:1567–1569.
33. Pye SM, Cortes J, Ault P, et al. The effects of imatinib on pregnancy outcome. Blood 2008;111:5505–5508.
34. Calzolari E, Bianchi F, Dolk H, Milan M. Omphalocele and gastroschisis in Europe: a survey of 3 million births 1980-1990. EUROCAT Working Group. Am J Med Genet 1995;58:187–194.
35. Soriano P. The PDGF alpha receptor is required for neural crest cell development and for normal patterning of the somites. Development 1997;124:2691–2700.
36. Robertson SC, Tynan J, Donoghue DJ. RTK mutations and human syndromes: when good receptors turn bad. Trends Genet 2000;16:368.
37. Russell MA, Carpenter MW, Akhtar MS, et al. Imatinib mesylate and metabolite concentrations in maternal blood, umbilical cord blood, placenta and breast milk. J Perinatol 2007;27:241–243.
38. Ali R, Ozkalemkas F, Kimya Y, et al. Imatinib use during pregnancy and breast feeding: a case report and review of the literature. Arch Gynecol Obstet 2009;280:169–175.
39. Kronenberger R, Schleyer E, Bornhauser M, et al. Imatinib in breast milk. Ann Hematol 2009;88:1265–1266.
40. Doll DC, Ringenberg QS, Yarbro JW. Antineoplastic agents and pregnancy. Semin Oncol 1989;16:337–346.
41. Rahman ME, Ishikawa H, Watanabe Y, Endo A. Carpal and tarsal bone development is highly sensitive to three antiproliferative teratogens in mice. Reprod Toxicol 1996;10:485–489.
42. Delmer A, Rio B, Bauduer F, et al. Pregnancy during myelosuppressive treatment for chronic myelogenous leukemia. Br J Haematol 1992;82:783–784.
43. Patel M, Dukes IA, Hull JC. Use of hydroxyurea in chronic myeloid leukemia during pregnancy: a case report. Am J Obstet Gynecol 1991;165:565–566.
44. Tertian G, Tchernia G, Papiernik E, Elefant E. Hydroxyurea and pregnancy. Am J Obstet Gynecol 1992;166(6 Pt 1):1868.
45. Jackson N, Shukri A, Ali K. Hydroxyurea treatment for chronic myeloid leukaemia during pregnancy. Br J Haematol 1993;85:203–204.
46. Sylvester RK, Lobell M, Teresi ME, et al. Excretion of hydroxyurea into milk. Cancer 1987;60:2177–2178.
47. Caplan SN, Coco FV, Berkman EM. Management of chronic myelocytic leukemia in pregnancy by cell pheresis. Transfusion 1978;18:120–124.
48. Broccia G, Casula P, Andria M. Chronic myelocytic leukemia in pregnancy: report of a case treated with leukapheresis. Tumori 1984;70:371–374.
49. Fitzgerald D, Rowe JM, Heal J. Leukapheresis for control of chronic myelogenous leukemia during pregnancy. Am J Hematol 1986;22:213–218.
50. Bazarbashi MS, Smith MR, Karanes C, et al. Successful management of Ph chromosome chronic myelogenous leukemia with leukapheresis during pregnancy. Am J Hematol 1991;38:235–237.
51. Ali R, Ozkalemkas F, Ozkocaman V, et al. Successful pregnancy and delivery in a patient with chronic myelogenous leukemia (CML), and management of CML with leukapheresis during pregnancy: a case report and review of the literature. Jpn J Clin Oncol 2004;34:215–217.
52. Girling JC, de Swiet M. Thromboembolism in pregnancy: an overview. Curr Opin Obstet Gynecol 1996;8:458–463.
53. Riyazi N, Leeda M, de Vries JI, et al. Low-molecular-weight heparin combined with aspirin in pregnant women with thrombophilia and a history of preeclampsia or fetal growth restriction: a preliminary study. Eur J Obstet Gynecol Reprod Biol 1998;80:49–54.
54. Ginsberg JS, Bates SM. Management of venous thromboembolism during pregnancy. J Thromb Haemost 2003;1:1435–1442.
55. Ginsberg JS, Greer I, Hirsh J. Use of antithrombotic agents during pregnancy. Chest 2001;119(1 Suppl):122S–131S.
56. Maher JE, Owen J, Hauth J, et al. The effect of low-dose aspirin on fetal urine output and amniotic fluid volume. Am J Obstet Gynecol 1993;169:885–888.
57. Owen J, Maher JE, Hauth JC, et al. The effect of low-dose aspirin on umbilical artery Doppler measurements. Am J Obstet Gynecol 1993;169:907–911.
58. Martinelli P, Martinelli V, Agangi A, et al. Interferon alfa treatment for pregnant women affected by essential thrombocythemia: case reports and a review. Am J Obstet Gynecol 2004;191:2016–2020.
59. Milano V, Gabrielli S, Rizzo N, et al. Successful treatment of essential thrombocythemia in a pregnancy with recombinant interferon-alpha 2a. J Matern Fetal Med 1996;5:74–78.

60. Pardini S, Dore F, Murineddu M, et al. Alpha 2b-interferon therapy and pregnancy—report of a case of essential thrombocythemia. Am J Hematol 1993;43:78–79.

61. Petit JJ, Callis M, Fernandez DS. Normal pregnancy in a patient with essential thrombocythemia treated with interferon-alpha 2b. Am J Hematol 1992;40:80.

62. Pons JC, Lebon P, Frydman R, Delfraissy JF. Pharmacokinetics of interferon-alpha in pregnant women and fetoplacental passage. Fetal Diagn Ther 1995;10:7–10.

63. Goh HG, Kim YJ, Kim DW, et al. Previous best responses can be re-achieved by resumption after imatinib discontinuation in patients with chronic myeloid leukemia: implication for intermittent imatinib therapy. Leuk Lymphoma 2009;50:944–951.

64. Rousselot P, Huguet F, Rea D, et al. Imatinib mesylate discontinuation in patients with chronic myelogenous leukemia in complete molecular remission for more than 2 years. Blood 2007;109:58–60.

65. Delmer A, Rio B, Bauduer F, et al. Pregnancy during myelosuppressive treatment for chronic myelogenous leukemia. Br J Haematol 1992;82:783–784.