The Effects of Imatinib on Pregnancy Outcome

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Abstract

Imatinib has now been in use for almost 10 years. Despite this cumulative experience, little is known about its effects on pregnancy and as a result there are few published data to facilitate the counselling of women who conceive whilst taking imatinib. The results we now present provide information which may be of use in such circumstances. Of 180 women exposed to imatinib during pregnancy outcome data are available for 125 (69%). Of those with known outcomes 50% delivered normal infants and 28% underwent elective terminations, 3 following the identification of abnormalities. There were a total of 12 infants in whom abnormalities were identified, 3 of which had strikingly similar complex malformations that are clearly a cause for concern. It appears that although the majority of pregnancies exposed to imatinib are likely to have a successful outcome, there remains a risk that exposure may result in serious fetal malformations.
Introduction

Imatinib mesylate, the first example of a molecularly targeted therapy, has completely revolutionised the treatment of chronic myeloid leukaemia, transforming a fatal disease with a median life expectancy of 6 to 7 years into a truly chronic condition for most patients. The efficacy of the drug coupled with its ease of administration and a low level of toxicity has resulted in many patients leading relatively normal lives. It has been estimated that imatinib could prolong the chronic phase of CML to an average of 12-15 years.\textsuperscript{1} This in turn has ramifications for the management of the current cohort of patients with CML and issues relating to quality of life therefore assume far greater importance. These include the ability to parent children.

Imatinib was first administered to patients with CML in June 1998 and it is estimated that there have now been 250,000 patient years of exposure to the drug (mostly in patients with CML). Despite this experience, there is still only limited information on the effects of imatinib on fertility and/or pregnancy. The manufacturer of imatinib recommends that women of child-bearing potential should avoid pregnancy whilst taking the drug. This recommendation is based on the results of animal studies, which showed imatinib to be teratogenic in rats in addition to general safety concerns surrounding the use of any new drug in pregnancy, and particularly one that targets to eliminate rapidly dividing cells.

The limited data available in the public domain on the outcome of pregnancies of patients exposed to imatinib consists mostly of case studies. Ault and colleagues were the first to publish on a series of 19 pregnancies, where either the male or female partner were undergoing treatment. Although three pregnancies ended with
spontaneous abortions, and one with an elective termination, 16 pregnancies were identified to be uneventful. We now report data on a series of 180 women who were exposed to imatinib during pregnancy.

**Materials and Methods**

We investigated the treatment, pregnancy and fetal outcomes of 180 women exposed to imatinib during pregnancy. Data were initially acquired from physicians who had reported either to Novartis, the Hammersmith Hospital in London or the MD Anderson Cancer Center in Houston. Many of these reports had been submitted retrospectively often a number of years previously and contained only the information disclosed at the time by the physician. Most of the information submitted to Novartis came from spontaneous reports. Of the 180 cases described only 28 patients (15.6%) were enrolled in clinical trials. Of these, 16 were from four separate trials initiated and led directly by Novartis and the remaining 12 cases originated from “third party studies”: the collection of pregnancy related data was not the primary objective of any of these studies. In those studies directly sponsored and coordinated by Novartis we identified 946 females of child-bearing age (defined for the purpose of this analysis as those aged between 17 and 50 years at the time of enrolment) who had been exposed to imatinib, giving an overall pregnancy rate of 16/946 or 1.69%. Of the 4 trials, the IRIS study involving newly diagnosed patients with CML in chronic phase had the highest incidence of pregnancy with 7/158 (4.43%) women of childbearing age becoming pregnant. Due to a lack of data from comparable studies we are unable to comment on whether this incidence is more or less than would be expected in such a trial. Having reviewed the initial reports we attempted to contact the relevant physicians by email, letter and phone, seeking additional information. We sought
details of the clinical indication, dose, timing of exposure to imatinib in relation to pregnancy, continuation or cessation of therapy, other medication, maternal age and outcome of the pregnancy with respect to both maternal and fetal issues. Unfortunately we were unable to obtain contact details for those physicians who had reported directly to Novartis as the release of such information to a third party is prohibited by the data protection act. Although efforts were made within the company to obtain the missing data much of the information pertaining to these cases remains incomplete. At the time of writing we still lack pregnancy outcome data for 55 of the 180 cases reported; the missing data are indicated in the results table and accompanying text. Of note, our data include the 10 cases recently reported by the M.D. Anderson Cancer centre. Information on the expected background incidence of spontaneous abortions and congenital abnormalities was obtained from published reports.

**Results**

Of the 180 women included in this study, the majority were being treated for CML (Table 1). The timing of exposure to imatinib by trimester was available for 146 cases (81%). Of these 103 (71%) were exposed in the first trimester (including 4 exposed in both the first and second trimesters). 38 (26%) received the drug throughout their pregnancy, i.e. the drug was not discontinued, and this figure includes women exposed up until the time of termination of pregnancy or spontaneous abortion (see Table 1 for outcome details). An additional 4 cases were exposed only after the first trimester.
Pregnancy Outcome: Outcome data are known for 125/180 pregnancies (69%). 63 pregnancies resulted in the birth of normal live infants equating to 50% of those with known outcome (KO) or 35% of all pregnancies. 35 women (28% with KO or 19.5% of total) underwent elective terminations, 3 following the identification of fetal abnormalities (see Table 2, infants 1-3). The remaining fetuses were either of unknown status or had no defects identified. 18 pregnancies (14.4% KO) ended in spontaneous abortion. Of the remaining 9 infants, there were 8 live-births and one still birth, all with congenital abnormalities (for details see Table 2 and text below)

Fetal Outcome: In total 12 pregnancies are known to have resulted in infants with fetal abnormalities (9.6% KO) and of these there were 8 live births, 1 stillbirth and 3 terminations (mentioned above). The dose (but not the exact duration) of imatinib taken by the mother is known for 10 of these cases. Unfortunately the data are insufficient to assess any potential relationship between cumulative dosage and the occurrence of fetal abnormalities. Of the infants born with congenital abnormalities, one had premature closure of the skull sutures (craniosynostosis) (imatinib stopped within the first few weeks of pregnancy, subsequent hydroxyurea until term), the second had hypoplastic lungs, exomphalos, duplex left kidney, absent right kidney, hemivertebrae and a right shoulder anomaly, the third infant had exomphalos, right renal agenesis and hemi-vertebrae (imatinib for 3 weeks and interferon at an unspecified time during pregnancy) and the fourth child had a small exomphalos and scoliosis. These last 3 cases are of note as the combinations of defects were strikingly similar. A further child was born with complex abnormalities including communicating hydrocephalus, cerebellar hypoplasia, and cardiac defects – this infant was born alive but died subsequently. A baby with a meningocoele was still born. The remaining 3 infants had relatively minor defects only (2 cases of hypospadias and 1
diagnosed with pyloric stenosis) (Table 2). There were no reports of maternal exposure to alcohol, tobacco or drug addiction during pregnancy in any of these cases. All concomitant medications are detailed in table 2 below and none of the mothers had received any high dose chemotherapy prior to their pregnancies.

Preclinical studies of fetal organogenesis in pregnant rats showed that imatinib is teratogenic, causing defects such as exencephaly, encephaloceles and deformities of the skull bones. Female rats given doses >45mg/kg (approximately equivalent to a human dose of 400mg/day based on body surface area) experienced significant post-implantation loss with increased fetal resorption, still births, non viable pups and early pup mortality. Doses higher than 100mg/kg resulted in total fetal loss (Novartis investigator’s brochure and Novartis clinical safety statement). Imatinib does not, however, appear to be mutagenic or clastogenic, i.e. it does not damage chromosomes. Accordingly, patients enrolled in clinical trials of the drug were advised not to conceive whilst undergoing treatment with imatinib, but inevitably some pregnancies did occur. Although in most cases we have no information regarding the timing of pregnancy in relation to the start date or dose of imatinib it is likely that the majority of women became pregnant whilst already receiving the drug rather than starting imatinib only after conception.

Our data show that a significant proportion (50% KO, 35% total) of pregnancies exposed to imatinib result in a normal outcome and a healthy infant. Although our results show a spontaneous abortion rate of 14.4% which is within the expected limits for the general population (spontaneous abortion rates of 10%-15%³) these data may be skewed by reporting bias and the absent outcome data for 55 cases. Of the 51 patients whose pregnancies were reported after a known outcome (as opposed to at
the time of confirmation of pregnancy) 11 (22%) ended in spontaneous abortion which may suggest an abortifacient effect. Perhaps of more concern are the 12 infants in whom congenital abnormalities were identified. Those with bony abnormalities are especially pertinent as similar bony defects including exencephaly, encephaloceles and deformities of the skull bones were observed in the rodent studies. The expected incidence of exomphalos in the general population is approximately 1 in 3-4,000 births and the finding of 3 cases out of 180 is far higher than would be predicted. It is of note that the infants with exomphalos all had a combination of very similar, quite complex defects which would be unlikely to occur by chance and make an imatinib-induced effect more probable.

Russell et al have recently reported that imatinib crosses the mature placenta inefficiently which might suggest that imatinib is unlikely to play a significant role in the development of fetal abnormalities. However the mechanism of nutrient supply to the fetus varies at different stages in gestation. Prior to 10 weeks there are no maternal arterial connections with the intervillous space and during the first few weeks of development it is thought most likely that the embryo obtains nutrients by simple diffusion from blood pooled in the trophoblastic lacunae. The uteroplacental and fetoplacental circulations and active transport mechanisms are established after the tenth week of gestation. These differences may account for varying effects according to the time of exposure to any individual drug.

However no information was provided about the ability of imatinib to cross the placenta during the first trimester, the period of greatest risk for fetal malformations. 10 of the 12 infants with abnormalities are known to have been exposed to imatinib during the 1st trimester (information unavailable for the remaining 2 cases). As the mechanism of action of imatinib involves inhibition of tyrosine kinases it is possible that the congenital abnormalities result from inhibition of members of this extensive
family. To date 90 human tyrosine kinases have been described,8 of which 58 are receptors. Embryonic development is under complex control and both c-KIT (a known target of imatinib) and members of the growth factor receptor families (e.g. EGFR) may play a role in placental development and angiogenesis. The craniosynostosis syndromes (e.g. Crouzon and Apert) are associated with mutations of members of the fibroblast growth factor receptor family9 however this is unlikely to be the underlying mechanism behind the defects seen as preclinical studies have demonstrated a very low affinity of imatinib for these receptors (FGFR-1 IC\textsubscript{50} 31.2 $\mu$mol/L as compared with IC\textsubscript{50} of 0.025 $\mu$mol/L for Bcr-Abl). A more likely candidate gene is the tyrosine kinase receptor PDGFR\textalpha (platelet derived growth factor receptor alpha) – a known target of imatinib to which the drug binds with high affinity (IC\textsubscript{50} of 0.1). Mice homozygous for null mutations in PDGFR\textalpha show combinations of birth defects including facial clefting, severe spina bifida occulta, cardiac defects, omphalocele, renal and urogenital anomalies and vertebral and rib fusion abnormalities.10,11 PDGFR\textalpha also appears to play a role in lung development as shown in studies with PDGFR\textalpha null mice that also carried a human YAC PDGFR\textalpha transgene with pups dying soon after birth due to lung hypoplasia.12

Discussion

The data in our retrospective study are mainly derived from spontaneous reports and the study is obviously affected by the lack of complete information for all pregnancies despite strenuous efforts to obtain this. The high rate of termination is understandable as it is likely that many of the pregnancies were unplanned. Despite these limitations we consider our findings to be representative of the expected outcome and feel that this report still represents the most comprehensive set of data on the effect of imatinib on pregnancy and is therefore very relevant to patients and physicians. Our data
indicate that concern is justified and that all female patients should be advised to avoid conception whilst taking imatinib. In the patient who does become pregnant whilst on treatment, balancing the risk to the fetus of continuing imatinib vs. the risk to the mother of interrupting treatment remains difficult. From the fetal perspective imatinib should be discontinued due to the potential risk of 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, considering termination should any significant abnormalities be identified. In these circumstances the couple should be made aware of potential risks particularly of 1st trimester exposure. Considerations include the wishes of the parents, the mother’s disease status, the availability of suitable alternative therapies and the ability to reinduce responses to imatinib after a prolonged period off treatment.

We have previously reported (2) 10 women (9 in CHR) who interrupted treatment with imatinib due to pregnancy. Of the 9 in CHR when the imatinib was stopped, 1 was in CCyR, 3 in partial cytogenetic response (1-34% Ph-positive metaphases) and 2 in minor cytogenetic response prior to interruption of therapy. Six of the nine had an increase in Ph-positive metaphases and five lost their CHR whilst off treatment. At a median of 18 months since restarting imatinib these 9 women were again in CHR and although all had a cytogenetic response this was complete in only 3. This might be considered a poor response as the rate of CCyR at 18 months in patients who received uninterrupted imatinib from diagnosis is 75%-90%. However as a group these 9 women showed improved responses to treatment following pregnancy when compared with their results pre-pregnancy. Reassurance that imatinib can be discontinued in some patients under certain favourable circumstances is provided by a recent report by Rousselot et al.13 Imatinib was discontinued in 12 patients who had
all been in complete molecular remission for a period of at least 2 years. Of these 12, 6 (50%) developed molecular relapse within 5 months of stopping imatinib therapy but the remaining 6 continued to have undetectable BCR-ABL transcripts at a median of 18 months follow-up. Of those who relapsed, the majority again achieved a complete molecular response within a relatively short period following reintroduction of imatinib.

In conclusion, exposure to imatinib during pregnancy might result in an increased risk of serious fetal abnormalities or spontaneous abortion. Women of child-bearing potential should use adequate contraception whilst taking imatinib. Imatinib should be avoided in pregnancy unless the risk of interrupting therapy is deemed by the patient’s physician to be unacceptable. In cases of accidental or planned pregnancy, risk/benefit evaluations must be carried out on an individual basis with careful counselling of both parents using the most recent data available. Alternative therapies for CML include interferon-α. Animal studies have shown this drug to be non-teratogenic in rats and rabbits, resulting in normal offspring but it has also been shown to have abortifacient effects in rhesus monkeys at doses of 90 and 180 times the recommended i.m. or s.c. dose of 2 million iu/m². In view of this the official recommendation is that IFN be avoided during pregnancy unless “the potential benefit justifies the potential risk to the foetus” (IntronA study of product characteristics). The treatment of CML during pregnancy remains a considerable clinical challenge. The intended establishment by Novartis of an international pregnancy registry may provide further information as experience with imatinib continues to grow.

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Author Contribution:
S. Pye wrote the manuscript and analysed/interpreted data. J. Cortes, H. Kantarjian, A. Hatfield and G. Rosti contributed data and reviewed the manuscript. R. Pilot and P. Ault collected and analysed data. J. Apperley was responsible for the conception and integrity of the manuscript.

Conflict-of-interest disclosure: A.H. and R.P. are both employees of Novartis, the company that manufactures imatinib. J.F.A. is a member of a national clinical advisory group and has received honoraria for independent presentations at regional and national company-sponsored meetings. JFA is grateful for support from the NIHR Biomedical Research Centre Funding Scheme. J.C. has received research funding from Novartis. G.R. has received honoraria from Novartis. S.M.P. has no conflicts of interest to declare. This work did not receive any external funding.
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**Table 1. Imatinib Pregnancies**

The table shows the outcome data for 180 pregnancies occurring in women receiving imatinib. It includes 4 women treated with imatinib for gastrointestinal stromal tumours (GIST), 28 treated for unknown indications and 5 for miscellaneous conditions. The data were collected by Novartis Pharmaceuticals (Basel, Switzerland).

<table>
<thead>
<tr>
<th>Pregnancy Outcome</th>
<th>Before LMP</th>
<th>1st Trimester</th>
<th>After 1st Trimester</th>
<th>Throughout Pregnancy</th>
<th>Unknown</th>
<th>Sub-total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous abortion</td>
<td>0</td>
<td>8</td>
<td>0</td>
<td>7</td>
<td>3</td>
<td>18</td>
</tr>
<tr>
<td>Elective termination – fetal defects</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1†</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Elective termination – normal or unknown</td>
<td>0</td>
<td>20</td>
<td>0</td>
<td>5</td>
<td>7</td>
<td>32</td>
</tr>
<tr>
<td>Stillbirth with fetal defects</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Live birth with congenital anomaly</td>
<td>0</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>Live birth without congenital anomaly</td>
<td>0</td>
<td>40†</td>
<td>1</td>
<td>18</td>
<td>4</td>
<td>63</td>
</tr>
<tr>
<td>Outcome unknown</td>
<td>1</td>
<td>27</td>
<td>3</td>
<td>7</td>
<td>17</td>
<td>55</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>1</strong></td>
<td><strong>103</strong></td>
<td><strong>4</strong></td>
<td><strong>38</strong></td>
<td><strong>34</strong></td>
<td><strong>180</strong></td>
</tr>
</tbody>
</table>

LMP, last menstrual period.

†Mother had concomitantly been receiving warfarin therapy. The results of a subsequent post-mortem revealed defects typical of warfarin embryopathy.

†Includes 4 cases with exposure in both 1st and 2nd trimesters.
Table 2. Summary of Congenital Defects Identified Following Maternal Exposure to Imatinib (n=12)

<table>
<thead>
<tr>
<th>Fetus No.</th>
<th>Trimester Exposure</th>
<th>Pregnancy Outcome</th>
<th>Maternal Age, years</th>
<th>Imatinib Dose (OD)</th>
<th>Other Medication</th>
<th>Fetal Abnormality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>First</td>
<td>Elective termination</td>
<td>29</td>
<td>300mg</td>
<td>None</td>
<td>• Abnormal ultrasound, elevated AFP</td>
</tr>
<tr>
<td>2</td>
<td>All</td>
<td>Elective termination</td>
<td>35</td>
<td>NK</td>
<td>Warfarin Paracetamol Levofloxacin Lorazepam Heparin Prochlorperazine</td>
<td>• Warfarin embryopathy: depressed nasal bridge, choanal stenosis, Dandy Walker cyst, ventricular septal defect, coarctation of the aorta, gastrochisis.</td>
</tr>
<tr>
<td>3</td>
<td>Unknown</td>
<td>Elective termination</td>
<td>37</td>
<td>400mg</td>
<td>Omeprazole</td>
<td>• Cleft palate, polydactyly</td>
</tr>
<tr>
<td>4</td>
<td>First</td>
<td>Stillbirth (34 weeks)</td>
<td>25</td>
<td>400mg</td>
<td>Hydroxyurea after 1st trimester Hydroxyurea</td>
<td>• Meningocele</td>
</tr>
<tr>
<td>5</td>
<td>First</td>
<td>Live birth</td>
<td>35</td>
<td>400mg</td>
<td>None</td>
<td>• Premature closure of skull sutures</td>
</tr>
<tr>
<td>6</td>
<td>First</td>
<td>Live birth</td>
<td>Unknown</td>
<td>NK</td>
<td>None</td>
<td>• Scoliosis, small exomphalos</td>
</tr>
<tr>
<td>7</td>
<td>First</td>
<td>Live birth (premature – week 30) Baby died after 45 minutes</td>
<td>25</td>
<td>400mg</td>
<td>NK</td>
<td>• Communicating hydrocephalus, cerebellar hypoplasia, atrial septal defect, overriding aorta, ascites, pericardial effusion</td>
</tr>
<tr>
<td>8</td>
<td>First</td>
<td>Live birth</td>
<td>27</td>
<td>300mg</td>
<td>Anagrelide and hydroxyurea (timing unknown)</td>
<td>• Hypospadias</td>
</tr>
<tr>
<td>9</td>
<td>First</td>
<td>Live birth</td>
<td>29</td>
<td>300mg</td>
<td>None</td>
<td>• Hypospadias</td>
</tr>
<tr>
<td>10</td>
<td>First</td>
<td>Live birth</td>
<td>35</td>
<td>400mg</td>
<td>Hydroxyurea after 1st trimester None</td>
<td>• Pyloric stenosis</td>
</tr>
<tr>
<td>11</td>
<td>First</td>
<td>Live birth</td>
<td>Unknown</td>
<td>400mg</td>
<td>None</td>
<td>• Hypoplastic lungs, exomphalos, left duplex kidney, right absent kidney, hemivertebrae and right shoulder anomaly</td>
</tr>
<tr>
<td>12</td>
<td>Unknown</td>
<td>Live birth (premature)</td>
<td>Unknown</td>
<td>400mg</td>
<td>Interferon</td>
<td>• Exomphalos, right renal agenesis and hemivertebrae</td>
</tr>
</tbody>
</table>
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