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Use of Granulocyte Colony–Stimulating Factor During Pregnancy in Women With Chronic Neutropenia

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Abstract

Objective—To report outcomes associated with the administration of granulocyte colony–stimulating factor (G-CSF) to women with chronic neutropenia during pregnancy.

Methods—We conducted an observational study of women of child-bearing potential with congenital, cyclic, idiopathic, or autoimmune neutropenia enrolled in the Severe Chronic Neutropenia International Registry to determine outcomes of pregnancies, without and with chronic G-CSF therapy, 1999–2014. Treatment decisions were made by the patients' personal physicians. A research nurse conducted telephone interviews of all enrolled U.S. women of child-bearing potential using a standard questionnaire. Comparisons utilized Fisher's exact test analysis and Student's *t*-test.

Results—One-hundred seven women reported 224 pregnancies, 124 without G-CSF therapy and 100 on chronic G-CSF therapy (median dose: 1.0 mcg/kg/day, range 0.02–8.6 mcg/kg/day). There were no significant differences in adverse events between the groups considering all pregnancies or individual mothers, e.g., spontaneous terminations (all pregnancies: no G-CSF 27/124, G-CSF 13/100; P=0.11, Fisher's exact test,), preterm labors (all pregnancies, no G-CSF 9/124, G-CSF 2/100, P=0.12,). A study with at least 300 per group would be needed to detect a difference in these events with 80% statistical power (alpha=0.05). Four newborns of mothers with idiopathic or autoimmune neutropenia not on G-CSF (4/101) had life-threatening infections, whereas there were

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no similar events (0/90) in the treated group, but this difference was also not statistically significant. (p=0.124). Adverse events in the neonates were similar for the two groups.

Conclusions—This observational study showed no significant adverse effects of administration of G-CSF to women with severe chronic neutropenia during pregnancy.

Introduction

Granulocyte colony–stimulating factor (G-CSF) is now widely used for the prevention of infections in patients with neutropenia and for mobilization of hematopoietic stem cells for transplantation.(1) Granulocyte colony–stimulating factor is also used on a long-term basis, administered daily or several times per week, to prevent infections in patients with cyclic, congenital, idiopathic, and autoimmune neutropenia, collectively referred to as severe chronic neutropenia.(2) As soon as G-CSF became available, patients and physicians began asking about the benefits and safety of its administration during pregnancy, questioning its effects on the health of both the mother and the neonate, in part because administered G-CSF crosses the placenta.(3)

The Severe Chronic Neutropenia International Registry was established in 1994 to study the natural history, treatments and outcomes for patients with severe chronic neutropenia, many of whom are now treated with G-CSF.(4) We surveyed the women of childbearing potential enrolled in SCNIR to determine the outcomes associated with the administration of granulocyte colony–stimulating factor (G-CSF) to women with chronic neutropenia during pregnancy.

Materials and Methods

The studies were conducted under the informed consent provisions of the institutional review board (IRB)/Human Subjects Division at the University of Washington.

Female patients older than 16 years of age living in the United States who were enrolled in the SCNIR were the participants in this study. The SCNIR enrolls patients with severe chronic neutropenia regardless of gender, ethnicity, social or economic status who have a series of at least three complete blood counts (CBC) showing blood neutrophil counts (ANC) less than 0.5×10^9/L in a three-month period. Patients are enrolled in four diagnostic categories: cyclic, congenital, or idiopathic, or autoimmune neutropenia. The cyclic category is confined to patients with serial blood counts showing peaks and nadirs of blood neutrophils occurring at approximately 21-day intervals, usually with nadir blood neutrophils $<0.2 \times 10^9$/L for 2–4 days. The congenital category includes patients with hereditary neutropenia most frequently attributable to mutations in gene for neutrophil elastase, *ELANE*, as well as patients with congenital neutropenia of other and unknown causes. Patients in the idiopathic or autoimmune category have acquired neutropenia of unknown cause with or without a positive test for anti-neutrophil antibodies. Patients with autoimmune diseases such as lupus erythematosus or rheumatoid arthritis or neutropenia due to cancer or cancer chemotherapy are excluded.

A research nurse experienced in the care of patients with chronic neutropenia interviewed all of the participants by telephone. The nurse used an IRB-approved questionnaire to obtain the patient's pregnancy history, usually in one session, but with follow-up calls as necessary. Patients were asked about all pregnancies and terminations as well as their state of health and medications both before and after enrollment in the SCNIR. The patients' general health, date of diagnosis of neutropenia, dates and doses for treatments with hematopoietic growth factors and other medications were part of the Severe Chronic Neutropenia International Registry records. (See the Appendix [Pregnancy Outcome Questionnaire] online at http://links.lww.com/xxx.)

Interviews were begun in 1999 in response to interest and concern about the outcomes and adverse events for pregnancies in women being treated with G-CSF. The research nurse initially interviewed all eligible patients (women of all ages if over 16 at the time the study started) over a period of several months. Thereafter, she contacted each new female patient older than 16 years to review her history of pregnancy and terminations at the time of enrollment. In addition, she contacted the patients annually as part of the regular follow-up program if the annual form indicated a pregnancy. The data were verified by a second data entry person and then the research nurse. The immunization history of the mothers (e.g., Tdap, influenza, etc) and medical records of the neonates (e.g., for extraction of physical examinations, vital signs and Apgar scores) were not available.

Student's *t*-test (unpaired) was used to compare maternal age and gestational age of the neonates for the treated and untreated patients. Welch's correction for different standard deviations did not affect the determination of significance. Normality of data sets was examined using the D'Agostino and Pearson omnibus K2 test; results from the non-parametric Mann Whitney test did not affect the determination of significance. Fisher's exact test was used to compare group data. All statistical tests were two-sided. P values <0.05 were considered statistically significant. Computations were made using GraphPad Prism 6 and GraphPad StatMate software.

Results

When this study began in 1999, there were 555 patients enrolled in the SCNIR. There were 268 patients under age 16 (142 males, 126 females) and 287 over age 16 (93 males, 194 females). To begin the study, 194 women (age 16 and above, without age limit) already enrolled were surveyed and followed up annually. As the younger previously enrolled patients reached age 16, they were included, as well as new patients entering the Registry. At the time of the analysis for this report, there were 1,294 enrolled patients, 469 under age 16 (239 males, 230 females) and 825 over age 16 (301 males, 524 females). All eligible patients were contacted and all disclosed pregnancies included. From this population we identified 124 pregnancies of mothers not exposed to G-CSF during pregnancy and 100 pregnancies of mothers exposed to G-CSF during pregnancy (Table 1). In the G-CSF treated group, 82/100 pregnancies were in patients on G-CSF during the first trimester. There were 20 elective terminations in the two groups; 8 of 20 were known to have occurred between 6–12 weeks gestational age, median 8 weeks. Data are not available on reasons for the elective abortions or the presence or absence of fetal congenital anomalies.

The cohorts with and without G-CSF treatment were similar, although there were small but statistically significant differences in the ages of the mothers, overall and for cyclic neutropenia. The age distribution for the no G-CSF cohort did not pass the D'Agostino & Pearson omnibus normality test (P=0.008). The mean age of this group (N=124) was 27.1+/5.78 (SD) years, range 18 to 41 years. For the G-CSF treated group (N=100) the ages were normally distributed (P=0.60); mean age was 28.8+/−5.13 years, range 16 to 44 years. Despite this, the test to compare unpaired Student's *t*-test yielded the most conservative results (largest P values) in comparing maternal and gestational ages of the two groups. As noted in Table 1, the dose of G-CSF used to treat severe chronic neutropenia is relatively low in these patients and most patients with chronic neutropenia, compared to that used routinely to promote marrow recovery after chemotherapy, i.e., approximately 5 mcg/kg/day.

Most of the women were Caucasian. The ethnicity of the two groups were: Not on G-CSF: Caucasian 98%, African-American-none, Hispanic-none, Asian-none, Native American 2%, Other-none; On G-CSF: Caucasian 92%, African-American 1.5%, Hispanic 5 %, Asian 1.5%, Other-none. Compared with the overall SCNIR population, there were relatively few patients with congenital neutropenia, and relatively few congenital patients not on G-CSF treatment, probably because the congenital group has the most severe problems with infections and are often treated with G-CSF beginning earlier in life.

Table 2 shows maternal complications with and without G-CSF analyzed for all pregnancies and by individual mother. During the observational period there were minor infections (e.g., cellulitis, mastitis, perirectal infections and pneumonia) and one life-threatening infection in each group (e.g., bacteremia, sepsis). There was no statistically significant difference between patient-reported preterm labor, preterm delivery, spontaneous abortions or the other complications listed in Table 2. Power analysis suggests that at least 300 patients per group would be needed to show a significant difference with 80% statistical power for alpha=0.05 for preterm labor or spontaneous abortions, based on these data. As expected, the spontaneous termination events occurred primarily in the first trimester in both groups (26/27, 96% no G-CSF, 11/12, 92% G-CSF treated). For the 11 women reporting preterm labor, five patients delivered before 34 weeks, all in patients not on G-CSF treatment. For the women delivering at 34 to 37 weeks, one patient was not on G-CSF and two were on treatment. The other three patients delivered at term. In the subanalyses we also examined treatment by trimesters. In the treated group, 18 patients were exposed to G-CSF only in the second or third trimester, not in the first trimester. The first-trimester data (124 patients not receiving any G-CSF during the pregnancy plus 18 not treated with G-CSF in the first trimester) showed that there was no difference in spontaneous terminations with or without G-CSF exposure (off G-CSF 27/142 vs. on G-CSF 13/82, p=0.59). For the women who reached the third trimester, there was also no difference in preterm labor with or without G-CSF (off G-CSF 9/97 vs. on G-CSF 2/87, p=0.06). If the analysis of outcomes is limited to 11 women with information for pregnancies both on and off G-CSF, there were a total of seven events, two spontaneous terminations and one preterm labor in women not on G-CSF, and three spontaneous terminations and one placenta previa in women on G-CSF.

Gestational ages were available for 96 neonates born to mothers not on G-CSF and 82 on G-CSF treatment (overall mean 37.7+/−0.47 weeks). The ages were not distributed normally in either group (omnibus normally test, $p<0.05$). There was a statistically significant difference in gestational ages (not on G-CSF: median 40 weeks, mean 38.6 +/− 4.7 (SD) weeks, on G-CSF: median 39 weeks, mean 36.6 +/−8.0 weeks, $P<0.05$). The gestational ages of the neonates born to women with idiopathic neutropenia were also significantly different, and, because this was the largest subgroup, account for most of the overall difference. (See Table 1) Birth weights were normally distributed for the patients not exposed to G-CSF ($P=0.11$) but not normally distributed for those exposed to G-CSF ($P=0.04$, omnibus normality test). There was no significant difference in the birth weights (no G-CSF 3.2+/−0.6 (SD) kg, G-CSF treated 3.3+/−0.7 kg, $P=0.514$). The data for preterm deliveries, i.e., before 37 weeks, is shown in Table 3, including listings of the preterm deliveries associated with neonatal neutropenia. Overall there were 15 cases of neonatal neutropenia, and only 4 of these cases were associated with preterm delivery. There was no statistical association of neonatal neutropenia with preterm delivery ($P=0.76$, Fisher's exact test).

The treatments and schedule for treatments were determined by the patients' physicians, not directed by the SCNIR. The schedule of G-CSF varied: daily 78%, alternate-day 5%, three days per week 8%, other 9%. The median dose of G-CSF was 1.0 mcg/kg/day (range 0.02 to 8.6 mcg/kg/day) and varied by diagnostic group, highest for congenital neutropenia (median 2.13 mcg/kg/day), lowest for autoimmune neutropenia (median 0.11 mcg/kg/day). In the treated group, the G-CSF dose for 13 patients with spontaneous terminations was median 0.4 mcg/kg/day, mean 0.98 mcg/kg/day (range 0.02 to 4.3 mcg/kg/day). For the other obstetric complications in 4 patients (preterm labor-2, abruption placenta-1, and placenta previa-1) G-CSF dose was median 2.2 mcg/kg/day, mean 2.6 mcg/kg/day and range 0.1 to 5.9 mcg/kg/day. The G-CSF dose for these patients was not significantly different from the G-CSF treated patients without these complications ($p=0.16$ and 0.56, respectively).

There were 101 live births resulting from the 124 pregnancies not exposed to G-CSF. (Table 4) Fifteen of these neonates, of which there were two sets of twins, had neonatal neutropenia (mothers' diagnoses were: congenital [2], cyclic [5], idiopathic [2], or autoimmune [2]). There were four serious infections in the neonates born to the mothers not on G-CSF (meningitis [1] and septicemia [3]). In addition, mothers not on G-CSF had neonates with other complications: cerebral palsy associated with prematurity (1), born with a collapsed lung (1) and a full-term neonate with respiratory distress, requiring intensive hospital care. (1). In the G-CSF treated group there were 90 live births in 100 pregnancies. Eighteen of these neonates, all single births, had neonatal neutropenia (mother's diagnoses: congenital [4], cyclic [5], idiopathic [4], and autoimmune [2]). Two of these neonates had minor infections, one neonate born at full term had respiratory distress syndrome associated with infection requiring intensive care, and two had congenital abnormalities (one esophageal fistula and one hydronephrosis). There was also one neonatal apnea associated with abruptio placentae at 36 weeks. The Apgar scores for the neonates and their medical records were not available. Five neonates had respiratory distress syndrome associated with prematurity, including one set of triplets, a clinical circumstance associated with respiratory distress syndrome delivered at 29 weeks. Two other neonates, all delivered early, i.e., 26 and 31 weeks due to mothers' idiopathic hypertension, also had respiratory distress. The triplets

made uneventful recoveries; the other two neonates recovered after prolonged intensive care. There were four life-threatening infections (4/101) without G-CSF, but no life-threatening infections (0/90) with G-CSF treatment (p=0.124), (See Table 4). For the four mothers of neonates with respiratory distress (respiratory distress with prematurity and at full term) G-CSF doses were 0.9, 1.7, 1.7 and 5.8 mcg/kg/day, median 1.7 mcg/kg/day, mean 2.53 mcg/kg/day, range 0.9 to 5.8 mcg/kg/day, doses not significantly different from those for mothers whose babies did not have these complications (p=0.55).

All of the mothers had at least three blood neutrophil counts before G-CSF that were less than 0.5×10^9/L, as required for enrollment in the Severe Chronic Neutropenia International Registry. These ANC values were: median 0.210×10^9/L, mean 0.237 +/− 0.018 [SEM] × 10^9/L. On G-CSF the ANCs were median ANC 2.497×10^9/L, mean ANC 3.646 +/− 0.242 [SEM] × 10^9/L. Hematological data for the neonates were not available.

Discussion

Granulocyte colony–stimulating factor is a natural cytokine regulating neutrophil production and deployment, and recombinant G-CSF is widely used to prevent neutropenia-related infections.(1–8) We conducted this observational study to assess outcomes associated with the administration of G-CSF to women with chronic neutropenia during pregnancy. We recognized the limits of this method of study, but determined that it would be valuable to collect and summarize this information for clinicians and researchers with interest in this field.(9–12).

The study included 124 pregnancies with exposure to G-CSF and 100 pregnancies with G-CSF treatment. The mothers in the treated group were significantly older (median 27 versus 29 years) and for the patients with cyclic neutropenia (25 versus 28 years) (See Table 1). We do not know if this might relate to starting G-CSF after failed attempts to have a pregnancy or if it is simply a chance finding of this small study. The number of pregnancies by diagnosis varied considerably; the largest group was the patients with idiopathic neutropenia, the group receiving the lowest median dose of G-CSF, as in other reports.(2) For this sub-group and overall, the gestational age of the G-CSF treated group was significantly lower, but the birth weights were not different. The biological basis and consequences of earlier births in women on G-CSF are not known, but deserve further study.

Analysis of adverse events (all events or events in individual women) revealed no significant differences for pregnancies with or without exposure to G-CSF (see Table 2). For some events it is possible that a study of approximately 300 patients per group, three times the size of the present study, might reveal significant differences. A much larger study would be needed to identify differences for other categories of adverse events.

Seventeen percent of the neonates born to the mothers in this study had neutropenia. Neonatal neutropenia is associated with prematurity(13), but statistical analysis shows no significant relationship for this small study in which 4/16 premature deliveries were associated with neutropenia and overall there were 33 cases of neonatal neutropenia. This suggests that other factors, e.g., inheritance of a causative genetic mutation (14), trans-

placental transfer of maternal antibodies(15), or allo-immunization because of maternal-paternal differences in neutrophil-specific antigens(16) may have been causal.

There were no statistically significant differences in complications among neonates in the two groups. Table 4 shows that there were four life-threatening infections in the babies of mothers not treated with G-CSF; a much larger study, probably 2 to 3 times the size of the present study would be required to show a significant difference or to be confident of no treatment effect.

We have previously examined the safety of G-CSF administration in severe chronic neutropenia.(17, 18) These studies show overall a very favorable safety profile. Patients with severe congenital neutropenia, however, are at risk of developing acute myeloid leukemia, with or without G-CSF treatment. We observed no events related to development of myeloid malignancies or other events in this study to indicate that G-CSF should be withheld from pregnant women. Based on the observations reported here and the wider experience of the SCNIR (19), we do not counsel neutropenic women on G-CSF against pregnancy and recommend genetic counseling for women with heritable forms of neutropenia. We also believe it is prudent to continue to long-term follow these patients and their children. In future studies we will broaden the scope of the maternal database and obtaining consent to collect data on their children to determine their long-term outcomes.

We are circumspect in interpreting these findings. This was an observational study of pregnancy in neutropenic women who self-reported the results of their pregnancies. There is limited data on the outcomes of the children. Other limitations include the size of the study population, the diversity of underling cases for neutropenia, the unevenness in the size of the individual groups, and potential for bias in self-reported data. While a randomized controlled trial of the use of this drug in women planning a pregnancy would be the ideal mechanism for describing the safety profile, such a study is unlikely to be done given the rarity of this disorder. Our interviews occurred over a 15-year period and we identified only 244 pregnancies. We feel that the observed improvement in maternal condition on G-CSF with no observed differences in pregnancy and neonatal complications is important information which could be used in counseling women with these disorders.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Characteristics of mothers treated and not treated with granulocyte colony–stimulating factor and their neonates

Diagnosis	All Participants and Pregnancies		Participants and Pregnancies without G-CSF treatment				Participants and Pregnancies with G-CSF treatment				
	# Patients (Pts)	# Pregnancies (Preg)	# Pts	# Preg	Mothers' Age at delivery mean (SD)	Neonates' GA at delivery mean (SD)	# Pts	# Preg	Mothers' Age at delivery mean (SD)	Neonates' GA at delivery mean (SD)	G-CSF Dose mcg/kg/day Median (Range)
Autoimmune	4	8	2	2	33 (0.48) (n=2)	40 (0.71) (n=2)	4	6	33 (5.54) (n=6)	38 (1.83) (n=4)	0.11 (0.23 – 4.6)
Congenital	15	21	3	4	26 (4.32) (n=4)	41 (1.29) (n=4)	12	17	29 (5.91) (n=7)	39 (2.89) (n=15)	2.13 (0.5 – 7.9)
Cyclic	29	74	15	35	25* (4.13) (n=35)	37 (7.64) (n=30)	20	39	28* (4.82) (n=39)	36 (10.1) (n=33)	1.1 (0.07 – 8.6)
Idiopathic	59	121	37	83	28 (6.19) (n=83)	40* (1.69) (n=60)	25	38	29 (4.89) (n=8)	37* (7.71) (n=30)	0.8 (0.02 – 5.7)
Total	107	224	57	124	27* (5.76) (n=124)	39* (4.65) (n=96)	61	100	29* (5.12) (n=100)	37* (8.0) (n=82)	1.0 (0.02 – 8.6)

* Denotes significant difference (P<0.05) between untreated and treated patients for the diagnostic category, unpaired Student's *t*-test

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Table 2

Maternal complications of mothers treated and not treated with granulocyte colony–stimulating factor during pregnancy

Clinical Events	All Pregnancies Not exposed to G-CSF	All Pregnancies exposed to G-CSF	Fisher's exact test (*P*)	Events in Individual Women Not Exposed to G-CSF	Events in Individual Women Exposed to G-CSF	Fisher's exact test (*P*)
Total Patients	---	---	---	57	61	---
Pregnancies	124	100	---	---	---	---
Spontaneous abortions	27	13	0.11	15	11	0.37
Pregnancies with live births	97	87		---	---	---
Preterm labor	9	2	0.12	5	2	0.26
Preterm rupture of membranes	1	0	1.00	1	0	0.48
Preterm delivery (<37 weeks)	10	10	0.64	8	9	1.00
Life-threatening infections (sepsis)	1	1	1.00	1	1	1.00
Minor infections (e.g., mastitis, sinus infection, perirectal abscess, cellulitis, pneumonia)	6	7	0.57	6	6	1.00
Severe thrombocytopenia	0	1	0.45	0	1	1.00
Abruptio placenta	0	1	0.45	0	1	1.00
Placenta previa	1	1	1.00	1	1	1.00

Table 3

Gestational age for the subgroups of patients overall and for pregnancies with early delivery of infants with neonatal neutropenia

Maternal Diagnosis	# Patients	# Pregnancies	Median Gestational Age Weeks at Delivery (range)	Gestational Age and Maternal Complications for Early Deliveries with Neutropenic Neonates (weeks)
Congenital	6	7	40 (38–42)	None
Cyclic	9	15	40 (29–40)	29, Preterm Labor; 36, Abruptio Placenta
Idiopathic	7	7	42 (35–43)	35, Preterm Labor
Autoimmune	3	4	39 (36–40)	36, Intrauterine growth restriction
Total	25	33	40 (29–43)	

Table 4

Neonatal complications of babies delivered from mothers treated and not treated with granulocyte colony–stimulating factor during pregnancy

Clinical Events	Babies of Mothers Not Treated with G-CSF	Babies of Mothers Treated with G-CSF
Total live births	101 (4 sets of twins)	90 (1 set of twins, 1 set of triplets)
Neonatal birth weights kg	mean (SD): 3.19 (0.64) range: 1.45–4.64 N = 83	mean (SD): 3.28 (0.67) range: 1.19–5.20 N = 76
Neonatal neutropenia	15 of 101 (15%)	18 of 90 (20%)
Life-threatening infection	4 of 101 (4%)	0 of 90 (0%)
Minor infection	1	2
Cerebral palsy associated with prematurity	1	0
Respiratory distress syndrome at full term	1	1
Respiratory distress syndrome associated with prematurity	0	5 (2 single neonates and 1 set of triplets)
Collapsed lung	1	0
Tracheal esophageal fistula	0	1 (exposed 1st trimester)
Hydronephrosis	0	1 (exposed in all 3 trimesters)
Neonatal apnea associated with abruptio placenta	0	1

*There are no statistical differences in complications among neonates delivered.