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Review

A systematic review of the fetal safety of interferon alpha

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ABSTRACT

Background: Interferon alpha (IFN) is an effective treatment for a variety of conditions including essential thrombocythemia (ET), chronic myelocytic leukemia, Hepatitis B and C. Because these conditions also occur in women of childbearing age who may become pregnant, information regarding the safety of this medication in pregnancy is essential. This systematic review attempts to summarize all published data on outcome of pregnancies exposed to IFN alpha, trying to differentiate between disease effect and drug effect.

Methods: Reports on the use of IFN alpha in human pregnancy and reports on essential thrombocythemia (ET) without use of any medication in pregnancy were identified by a systematic search of the medical literature. We were able to locate only case reports of IFN alpha exposure in pregnancy, of whom 40 out of 63 were diagnosed with ET. We also collected randomly 71 cases (more cases were available in the literature) that were diagnosed with ET due to different etiologies, but who had not received any medication in pregnancy.

Results: Among the 63 IFN alpha exposures in pregnancy, the mean maternal age was 30 ± 6 years and the mean full term babies' weight was 3096 ± 463 g. Mean gestational age at delivery was 37 ± 3 weeks. There were 55 single and 4 twin pregnancies. No cases of major malformations or stillbirths were reported. There was one case of spontaneous abortion and 13 preterm deliveries (20% of all exposed cases).

Among the 71 cases with untreated ET in pregnancy of different etiologies, 46 (65%) had early (within the first 12 weeks of pregnancy) or late (13–20 weeks of gestation) pregnancy loss. There were also 3 cases (4%) of stillbirth and 4 cases (5.6%) of preterm delivery. Only 18 women (25%) delivered healthy term babies.

Conclusions: The results of our systematic review suggest that IFN-α does not significantly increase the risk of major malformation, miscarriage, stillbirth or preterm delivery above general population rates. It is also possible that IFN-α may have a protective effect against pregnancy loss in cases of ET.

Contents

1. Background

Interferon (IFN) alpha was the first cytokine discovered 50 years ago as, with an extensive range of immunomodulatory and antiangiogenic properties, leading to its use in the treatment of malignancies [1]. IFNs are endogenous glycoproteins produced released by lymphocytes in response to pathogens or tumor cells. IFN-α plays a significant role in the control of viral infections, exerting its antiviral effects through activation of hundreds of interferon-induced/stimulated genes (ISGs) [2]. Endogenous IFN-α level gradually increase with age, peaking in young adults and gradually declining thereafter [3].

IFN-α is used clinically in the treatment of infectious diseases including Hepatitis B and C, genital warts, Herpes simplex and HIV.

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Table 1
Indications for IFN-α use in pregnancy.

Disease	Frequency	Percent%
CML (chronic myelocytic leukemia)	11	18.6
ET (essential thrombocythemia)	40	67.7
Hep C (hepatitis C)	4	6.7
HCL (hairy cell leukemia)	2	3.3
Hep C + HIV (hepatitis C & human immune deficiency virus)	1	1.5
MM (multiple myeloma)	1	1.5
Total	59	100

It is also used in hemato-oncological conditions, including essential thrombocythemia (ET), chronic myelocytic leukemia (CML), hairy cell leukemia, Kaposi's sarcoma, multiple myeloma, Non Hodgkin lymphoma, cutaneous T cell lymphoma, malignant melanoma, basal cell carcinoma, and polycythemia vera. In addition, IFN-α is used in conditions such as benign hemangioma, chronic inflammatory demelinating polyneuropathies, and sub-retinal neovascular proliferative diseases [4–40] (Table 1).

Although some of the conditions treated with IFN-α (e.g. CML and multiple myeloma) occur in older age groups, many of them may occur in young adults, including women of childbearing age. Because patients of childbearing age may become pregnant, information regarding the safety of IFN-α in pregnancy is essential. This systematic review attempts to summarize all published information on outcome of pregnancy following exposure to IFN-α, and, whenever possible, comparing outcome between treated and untreated pregnant patients.

2. Methods

Pub Med, EMBASE, and Google Scholar were searched using the words "pregnancy" and "IFN-α". References of included papers were further screened to identify reports that could have been missed by the initial search. No cohort or case control studies on IFN-α exposure in pregnancy could be located. Hence this review includes all case reports of pregnancies exposed to IFN-α

Because the drug is commonly used in essential thrombocythemia (ET), Pub Med, EMBASE, and Google Scholar were searched using the words "pregnancy" and "essential thrombocythemia". 71 untreated ET cases were randomly identified from different papers [41–58] (more cases were available in the literature). This group was used to compare outcome of pregnancy among ET patients treated with IFN-α and those not receiving any drug therapy.

Descriptive statistics and chi square tests were used when appropriate.

3. Results

A total of 63 pregnancies exposed to IFN-α were identified [28–40]; 43 (68%) received IFN-α at least during the first trimester, 47 (74%) at least in the second trimester, 48 (76%) at least during the third trimester; 37 (60%) used IFN-α throughout pregnancy.

The mean maternal age was 30 ± 6 years and the mean weight of full term babies was 3096 g. There were 55 single and 4 twin pregnancies. No major malformations and no stillbirths were reported in any of the cases. There was one spontaneous abortion described and 13 preterm deliveries (20% of all cases). Among the 37 babies for whom gender information was provided, 14 were males and 23 females (Table 2). The various indications for IFN treatment are presented in Table 1.

Among the identified 71 ET cases who had not received IFN-α during pregnancy, 46 (65%) resulted in an early (within the first 12 weeks of pregnancy) or late (between 13 and 20 weeks of pregnancy) miscarriages, as compared to only one (2.5%) among the 40 IFN-α – treated ET ($p < 0.0001$). There were 3 stillbirths and 4 preterm deliveries among the untreated ET, and 18 only (25%) untreated ET cases had healthy term babies [41–58,60] (Table 3).

Table 2
Patients' characteristics.

Total	63 pregnancies in 59 women
Maternal age	Average 30 ± 6 years
First trimester	43 (5 missing info)
Second trimester	47 (5 missing info)
Third trimester	48 (5 missing info)
Whole pregnancy	38 (5 missing info)
Single pregnancy	55
Twins	4
Major malformation	0
Spontaneous abortion	$N = 1$
Stillbirth	$N = 0$
Preterm delivery	$N = 13$ (20%)
Gender	14 males, 23 females in 37 cases that gender was identified & in 26 cases gender was not identified.
SGA	8 (from 41 pregnancies)

Table 3
Outcomes of 71 pregnancies with untreated ET (essential thrombocythemia).

Total number of pregnancies	71
Early & late abortion	46 (64%)
Still birth	3 (4.2%)
Preterm delivery	4 (5.6)%
Major malformation	0
Normal term babies	18 (25%)

4. Discussion

Our systematic review of published cases of IFN-α use in pregnancy did not identify any published reports of major malformations. While it is possible that isolated cases of malformations associated with this treatment may have gone unreported, based on the number of cases collected ($N = 63$) without problems, it is unlikely that a significant proportion of exposures to IFN-α would result in congenital malformations. Moreover, case reports tend to over report adverse outcome rather than normal pregnancies.

In an attempt to further understand the safety of IFN-α in pregnancy, we have selected the subset of cases of pregnant women treated for ET, the most common indication for IFN-α use in pregnancy (40 out of 59 cases who used IFN-α in our review). ET is associated with conditions such as thrombus formation and bleeding that may jeopardize the patient's life, or lead to pregnancy loss. The published literature indicates that ET in pregnancy leads to high rates of miscarriage in untreated cases [41–57]. It is conceivable that untreated patients suffered from less severe disease, yet they had more pregnancy loss than among those receiving IFN-α. This strengthens the evidence that using IFN-α in more severe cases of ET in pregnancy render a protective effect against pregnancy loss.

Several clinical trials have shown the effectiveness of IFN-α in bcr-abl-negative myeloproliferative neoplasms, especially in ET [1]. Twenty percent of ET cases are diagnosed before the age of 40. This together with the current trend of delaying pregnancy may explain why ET in pregnancy has become an increasingly frequent clinical problem [23–25]. Indeed, in our review of all 63 reports of IFN-α exposure in pregnancy, almost 90% of cases used this medication for ET and chronic myelocytic leukemia (CML).

There was not a single major malformation reported in this review out of 43 first trimester exposure, and only one case of spontaneous abortion was reported, as compared to 64% miscarriages among untreated ET. Hence, this systematic review suggests that it is unlikely that IFN-α increases the risk of major malformation above general population rate. Also, the low rates of reported miscarriages in the IFN-α treated ET patients (1.5%; 1/63), as compared to the 64% rate reported in the untreated ET patients, strongly suggests a protective effect of IFN-α against early and late fetal loss associated with ET.

Preterm birth (<37 weeks) complicates 12.5% of all deliveries in the USA [58]. The rate of preterm delivery in the IFN-α exposed cases was 20%. This difference could be caused by inclusion of four twin pregnancies with preterm deliveries [59]. If these 8 preterm twin babies are excluded from the analysis, the rate of preterm delivery decreases to 7.5%, well within the expected incidence.

A major weakness of the review is its reliance only on case reports and on a relatively small number of exposed cases. However, the lack of any cohort study necessitated analysis of existing data, namely case reports. In addition, there is lack of information regarding the severity of ET in treated versus untreated patients, which could be a confounding factor. While this reality limits the strength of any conclusion, the present analysis does show some very important trends.

It is well documented that retrospectively collected case series tend to over-report adverse fetal outcome [60]; hence, the lack of reported adverse fetal outcomes in the series collected in this systematic review, combined with the sharply lower reported miscarriage rate among pregnant women diagnosed with ET who received IFN-α in pregnancy are reassuring. These results may help reassure women who need IFN-α during pregnancy. However, it is advisable that women treated with IFN-α during pregnancy be reported to a pregnancy registry to ensure larger numbers and more robust results.

References

[1] Kiladjian JJ, Chomienne C, Fenaux P. Interferon-alpha therapy in bcr-abl-negative myeloproliferative neoplasms. Leukemia 2008;22(November (11)):1990–8.
[2] Lenschow DJ, Giannakopoulos NV, Gunn LJ, Johnston C, O'Guin AK, Schmid RE. Identification of interferon-stimulated gene 15 as an antiviral molecule during Sindbis virus infection *in vivo*. J Virol 2005;79(November (22)):13974–83.
[3] Shiozawa S. Interferon alpha (IFN alpha) treatment for Sjögren's syndrome. Nippon Rinsho 2006;64(July (7)):1345–53.
[4] Smylie M, Claveau J, Alanen K, Tailleger R, Gearge R, Wong R, et al. Canadian expert panel on malignant melanoma. J Cutan Med Surg 2009;13(March–April (2)):55–73.
[5] Griesshammer M, Struve S, Barbui T. Management of Philadelphia negative chronic myeloproliferative disorders in pregnancy. Blood Rev 2008;22:235–45.
[6] Koh LP, Devendra K, Tien SL. Four pregnancies in 2 patients with essential thrombocythemia. Ann Acad Med Singapore 2002;31:353–6.
[7] Martinelli P, Martinelli V, Agangi A, Maruott GM, Paladini D, Ciancia R, et al. Inteferon alpha treatment for pregnant women affected by essential throbocythemia: case report and review. Am J Obstet Gynecol 2004;191(December (6)):2016–20.
[8] Beressi AH, Tefferi A, Silverstein MN, Petit RM, Hoagland HC. Outcome analysis of 34 pregnancies in women with essential thrombocythemia. Adv Intern Med 1995;155:1217–22.
[9] Cincotta R, Higgins JR, Tippett C, Gallery E, North R, McMahon LP, et al. Management of essential thrombocythemia during pregnancy. Aust N Z J Obstet Gynaecol 2000;40:33–7.
[10] Melillo L, Tieghi A, Candoni A, Radaelli F, Ciancia R, Speccia G, et al. Outcome of 122 pregnancies in essential thrombocythemia patients: a report from Italian registry. Am J Hematol 2009;84(October (10)):636–40.
[11] Barbui T, Barosi G, Grossi A, et al. Practice guidelines for the therapy of essential thrombocythemia. A statement from the Italian Society of Hematology, the Italian Society of experimental hematology and the Italian Group for bone marrow transplantation. Hematologica 2004;89:215–32.
[12] Harrison C. Pregnancy and its management in the Philadelphia negative myeloproliferative diseases. Br J Haematol 2005;129:293–306.
[13] Iwashita T, Fujitani M, Yamamoto Y, Katsurada T, Yoshida Y. Interferon alpha treatment of essential thrombocythemia during pregnancy. Intern Med 2006;45:1879, doi: 10.2169/internal medicine.
[14] Milano V, Gabrielli S, Rizzo N, Vianelli N, Gugliotta L, Orsini LF, et al. Successful treatment of essential thrombocythemia in a pregnancy with recombinant interferon α2α. J Matern Fetal Med 1996;5:74–8.
[15] Nevruz O, Goktolga U, Avcu F, Ozsari L. Multiple gestation in an essential thrombocythemia patient treated with interferon alpha. Acta Obstet Gynecol Scand 2007;86(7).
[16] Mesquita MM, Pestana A, Mota A. Successful pregnancy occurring with interferon alphatherapy in chronic myeloid leukemia. Acta Obstet Gynecol Scand 2005:84.
[17] Ozaslan E, Yilmaz R, Simsek H, Tatat G. Interferon therapy for acute Hepatitis C during pregnancy. Ann Pharmacother 2002;36(November).
[18] Baykal C, Al A, Demirol A, Bozdag G, Ayhan A. Twin pregnancy after ICSI in a patient with ovarian cancer complicated with materna hepatitis C: case report. Eur J Obstet Gynecol Reprod Biol 2002;102(April (1)):96–7.
[19] Mubarak AAS, Kakil IR, Awidi A, Al-Homsi U, Fawzi Z, Kelta M, et al. Normal outcome of pregnancy in chronic myeloid leukemia treated with interfero α in 1st trimester: report of 3 cases and review of the literature. Am J Hematol 2002;69:115–8, doi:10.1002/ajh.1191.
[20] Roth MS, Foon KA. Alpha interferon in the treatment of hematologic malignancies. Am J Med 1986;81:871–82.
[21] Al Bahar S, Pandita R, Nath SV. Pregnancy in chronic myeloid leukemia patients treated with alpha interferon. Int J Gynecol Obstet 2004;85:281–2.
[22] Vantroyen B, Vanstraelen D. Management of essential thrombocythemia during pregnancy with aspirin, interferon alpha 2a and no treatment. Acta Haematol 2002;107:158–69.
[23] Griesshammer M, Bergmann L, Pearson TC. Fertility, pregnancy and the management of myeloproliferative disorders. Baillieres Clin Haematol 1998;11:859–74.
[24] Griesshamme M, Grunewald M, Jan JM. Acquired thrombophilia in pregnancy: essential thrombocythemia. Semin Thromb Hemost 2003;29(2).
[25] Griesshamme M, Heimpel H, Pearson TC. Essential thrombocythemia and pregnancy. Leuk Lymphoma 1996;22(Suppl. 1):57–63.
[26] Mishkin D, Deschenes M. Conception soon after discontinuing interferon/ribavirin therapy: a successful outcome. Am J Gastroenterol 2001; 96(7).
[27] Lebon P, Girard S, Thepot F, Chany C. The presence of alpha interferon in human amniotic fluid. J Gen Virol 1982;59:393–6.
[28] Baer MR, Ozer H, Kenneth A. Interferon alpha therapy during pregnancy in chronic myelogenous leukemia and hairy cell leukaemia. Br J Haematol 1992;81:160–7.
[29] Williams JM, Schlesinger PE, Gray AG. Successful treatment of essential thrombocythaemia and recurrent abortion with alpha interferon. Br J Haematol 1994;88(November (3)):647–8.
[30] Radi ML, Barbone E, Girolami A. Normal pregnancy and delivery in essential thrombocythemia even without interferon therapy. Am J Hematol 1994;45(March (3)):270–1.
[31] Petit JJ, Callis M, Fernandez de Sevilla A. Normal pregnancy in a patient with essential thrombocythemia treated with interferon a2b. Am J Hematol 1992;40:80.
[32] Pardini S, Dore F, Murineddu M, Bontigli S, Longinotti M. Alpha 2b interferon therapy and pregnancy – report of a case of essential thrombocythemia. Am J Hematol 1993;43(May (1)):78–9.
[33] Baer MR. Letter to the editor: normal full term pregnancy in a patient with chronic myelogenous leukemia treated with a interferon. Am J Hematol 1991;37:66.
[34] Pardini S, Careddu MF, Dore F, Bonfigli S, Gigliotti B, Longinotti M. Essential thrombocythemia and pregnancy. Haematologica 1995;80(July–August (4)):392–3.
[35] Delage R, Demers C, Cantin G, Roy J. Treatment of essential thrombocythemia during pregnancy with interferon a. Obstet Gynecol 1996;87(May (5Pt 2)):814–7.
[36] Cincotta R, Higgins JR, Tippett C, Gallery E, North R, McMahon LP, et al. Management of essential thrombocythemia during pregnancy. Aust N Z Gynecol 2000;40(1):33–7.
[37] Skata H, Karamitsos J, Kundaria B, Disaia PJ. Case report of interferon alpha therapy for multiple myeloma during pregnancy. Am J Obstet Gynecol 1995;172(January (1 Part 1)):217–9.
[38] Fritz M, Vats K, Goyal RK. Neonatal lupus and IUGR following alpha- interferon therapy during pregnancy. J Perinatol 2005;25:552–4.
[39] Hiratsuka M, Minakami H, Koshizuka S, Sato I. Administration of interferon-alpha in pregnancy: effects on fetus. J Perinat Med 2000;28:372–6.
[40] Delage R, Demers C, Caantin G, et al. Treatment of essential thrombocythemia during pregnancy with interferon alpha. Obstet Gynecol 1996;87:814.
[41] Gangat N, Wolanskyi AP, Schwa Schwager S, Tefferi A. Acquired thrombophilia in pregnancy: essential thrombocythemia. Semin Thromb Hemost 2003;29(April (2)):205–12.
[42] Bellucci S, Janvier M, Tobelem G, et al. Essential thrombocythemias: clinical evaluation and biological data. Cancer 1986;58:2440.
[43] Kaibara M, Kobayashi T, Matsumoto S. Idiopathic thrombocythemia in pregnancy: a report of a case. Obstet Gynecol 1985;65:18s.
[44] Mercer B, Drouin J, Jolly E, et al. Primary thrombocythemia in pregnancy: a report of two cases. Am J Obstet Gynecol 1988;159:127.
[45] Falconer J, Pineo G, Blahey W, et al. Essential thrombocythemia associated with recurrent abortions and fetal growth retardation. Am J Hematol 1987;25: 345.
[46] Johnson PM, Davis JM, Rand J. Thrombocythemia and recurrent miscarriage. Br J Obstet Gynaecol 1980;96:1231.
[47] Snethlage W, Ten-case JW. Thrombocythemia and recurrent late abortions: Normal outcome of pregnancies after antiaggregatory treatment: case report. Br J Obstet Gynaecol 1986;93:386.
[48] Lishner M, Amoto D, Farine D. Different outcomes of pregnancy in women with essential thrombocytosis. Isr J Med Sci 1993;29:100.
[49] Okayasu N, Murta M, Ueda A, et al. Primary thrombocythemia and myocardial infarction in a 26 year old woman with normal coronary arterigram. Jpn Heart J 1981;22:439.
[50] Murphy S. Thrombocytosis and thrombocythaemia. Clin Haematol 1983;12:89.
[51] Hoagland HC, Silverstein MN. Primary thrombocythemia in the young patient. Mayo Clin Proc 1978;53:578.
[52] Beard J, Hillmen P, Anderson CC, et al. Primary thrombocythemia in pregnancy. Br J Haematol 1991;177:371.

[53] Ferrai A, Veneziano S, Neri V, et al. Un caso gradidanzo Condetta a termine senza complicanze da una giovane affetta da thrombocythemia primitive. Recenti Prog Med 1986;77:183.
[54] Minkhorst AG, Novakova IRO, Van Dongan PWJ. Idiopathic thrombocythemia and pregnancy: a case report. Eur J Obstet Gynecol Reprod Biol 1991;40:237.
[55] Rondi ML, Barbone E, Rossi L, et al. Essential thrombocythemia and pregnancy: a report of six normal pregnancies in 5 untreated patients. Obstet Gynecol 1994;83:915.
[56] Griesshammer M, Grünewald M, Michiels JJ. Acquired thrombophilia in pregnancy: essential thrombocythemia. Semin Thromb Hemost 2003;29(April (2)):205–12.
[57] Harrison CN. Current trends in essential thrombocythaemi. Br J Haematol 2002;117:796–808. Summary of 220 reported pregnancies in women with ET.
[58] Ananth CV, Vintzileos AM. Epidemiology of preterm birth and its clinical subtypes. J Matern Fetal Neonatal Med 2006;19(December (12)): 773–82.
[59] Stock S, Norman J. Preterm and term labor in multiple pregnancies. Semin Fetal Neonatal Med 2010;15(December (6)):336–41.
[60] Bar-Oz B, Moretti ME, Mareels G, Van Tittelboom T, Koren G. Reporting bias in retrospective ascertainment of drug-induced embryopathy. Lancet 1999;354(November (9191)):1700–1.