

REVIEW ARTICLE

Neurofibromatosis type-1 and pregnancy: a review

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ABSTRACT

Introduction: Neurofibromatosis type-1 (NF1) is an autosomal dominant tumor predisposition genetic disease, with diverse expression that can affect almost any organ system. Pregnancy among patients with NF1 is remarkably stated as at high risk of complications. **Purpose:** To present a short and comprehensive review of the literature concerning the relation between pregnancy and NF1. **Materials and Methods:** Articles identification through electronic databases was performed by using key terms: pregnancy, neurofibromatosis, neurofibromatosis type-1. **Pregnancy issues:** Most of the relevant citations are edited to announce case reports or studies based on few patients' samples. Since,

authors in the past frequently delivered conflicting results, new retrospective studies, based on larger patient groups and matched with control groups, showed up over the last decade, to support that pregnancy in patients with NF1 is actually at high risk of complications. **Conclusions:** Pregnancy in women with NF1 seems to be notably at higher risk of complications, especially hypertension/preeclampsia, IUGR, stillbirth, preterm labor, cesarean section and maternal tumor growth tendency aggravation. Despite, most authors strongly recommend close monitoring of these patients during pregnancy, a normal outcome seems to be more probable to occur.

KEY WORDS

Neurofibromatosis, neurofibromatosis type-1, NF1, pregnancy

Introduction

Neurofibromatosis type-1 (NF1), also known as Von Recklinghausen's disease, is a relatively common multisystem genetic autosomal dominant disorder, caused by mutation of the homonymous gene (NF1) located on chromosome 17 [1,2]. Mutations of the NF1 gene creates a

syndrome characterized mainly by the development of multiple neurofibromas, café-au-lait spots (Fig. 1), Lisch nodules (iris hamartomas), freckling of the axillar or inguinal regions and optic gliomas [2]. The worldwide birth incidence of the disorder is 1:2500 – 1:3500, regardless of ethnicity or race, with over two million cases globally

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[3,4]. Half of the patients have a new NF-1 gene mutation while the other half have inherited the disorder [5-7].

Pregnancy, due to hormonal changes associated, might cause an increase in the size of already existing neurofibromas and appearance of new ones [8,9]. The majority of women with NF1 have healthy pregnancies, but need careful monitoring as early diagnosis and treatment results in better outcome [10,11]. The reported incidence of NF1 in pregnancy varies from 1:5000 to 1:18500 [12]. Fetal complications in women affected include spontaneous miscarriage, preterm delivery, intrauterine growth retardation and stillbirth, while maternal complications include, mostly, hypertensive and cerebrovascular disease [13,14].

Neurofibromatosis type 1 (NF1) is one of the most frequent dominantly inherited tumor predisposition genetic disorder, caused by mutation of the NF1 gene on chromosome 17q [1]. The NF-1 gene is responsible for the production of a large protein, called Neurofibromin, which acts as a tumor suppressor protein due to its function as negative regulator of Ras cellular pathways [15]. This tumor-suppressor protein is widely expressed throughout the body including the brain, kidney and blood vessels [16,17]. A myriad of possible mutations of the NF1 gene leads to abnormal growth and division in multiple body systems. For instance, loss of heterozygosity (LOH) in the melanocyte lineage results in cafe au lait macules (CALMs), hyperpigmented patches of skin present in nearly all patients, and LOH in the Schwann cell lineage leads to the development of neurofibromas [2,3,18-21]. NF1 syndrome has markedly variable clinical expression, characterized by the development of multiple neurofibromas, café-au-lait spots, Lisch nodules (iris hamartomas), freckling of the axillar or inguinal regions, bone deformities, learning disabilities, attention deficit/hyperactivity disorder, gradual hearing loss, ringing in the ears, poor balance, headaches [10]. The classic NF1-associated tumours include malignant peripheral nerve sheath tumours (MPNSTs), optic pathway gliomas, rhabdomyosarcomas, neuroblastomas, juvenile myelomonocytic leukaemias, gastrointestinal stromal tumour (GIST), phaeochromocytomas and breast cancer [22,23]. Phenotypic expression of the NF1 gene mutation is extremely heterogeneous, therefore molecular diagnosis cannot predict clinical gravity of the disease [1].

The aim of this review is to evaluate the available evidence on how pregnancy can be affected by Neurofibro-



Fig 1. Freckling and cafe au lait spots

matosis type 1 disorder and contrarily in what way this genetic disease can be aggravated by a pregnancy hormone condition.

Pregnancy Issues

In the past, the majority of the articles available on the outcome of pregnancy in patients affected by neurofibromatosis type 1 was made of case reports. That fact created an impression of a high rate of maternal and fetal complications as well as disease worsening at the point that, some authors have recommended termination of pregnancies and sterilization of women with NF1 [24]. Lately, retrospective studies of patient groups, made of women with NF1 during pregnancy and matched with control groups, have given a clearer picture of the relation between pregnancy and NF1 disease.

Pregnant women affected by NF1 is believed by many

Study	Study purpose	Sample Size	Maternal manifestations	Maternal Complications	Fetal Complications
Swapp & Main, 1973 ²⁵	outcome of 24 pregnancies in 10 NF pts	10 wo, 24 pregnancies	Café-au-lait spots; axillary freckling; nodular skin lesions (neurofibromas)	Hypertension (5 already hypertensive at 1st visit/to the end of their pregnancies all wo shown significant rise of mean BP; both pigmented & nodular lesions increased in size & number during pregnancy in all pts, in 7 of them there was considerable regression of nodular lesions following delivery)	Not reported
Jarvis & Crompton, 1978 ²⁶	outcome of 27 pregnancies in 10 NF pts	10 wo, 27 pregnancies	Histologically proven NF	Hypertension (2/27)	Spont abortion 4/27; therapeutic abortion 1/27; stillbirth 1/27
Weissman et al, 1993 ¹²	the experience with 34 pregnancies in 9 NF pts	9 wo, 34 pregnancies	Café-au-lait spots; multiple neurofibromas all over the body	None	Spont abortions of 1st trimester ; stillbirths 8.7%; IUGR 13%; high rate of CS 26%
Hadi, 1995 ²⁷	outcome of 14 pregnancies in 8 NF pts	8 wo, 14 pregnancies	Café-au-lait spots; cutaneous neurofibroma; mental deficiency; seizures; ganglia neuroma; glioblastoma of the brain; scoliosis; oral tumor	Hypertension; maternal & fetal death due to intracranial hemorrhage after recurrence of a glioblastoma of the basal ganglia previously resected	Spont abortions 7.1%; therapeutic abortions 42.8%; IUGR 1 fetus; stillbirth 1 fetus; preterm labor 28.6%; live birth infants 50%
Dugoff & Sujansky, 1996 ¹¹	Retrospective study of 247 pregnancies in 105 wo with NF1	105 wo, 247 pregnancies	Pts already diagnosed with NF1	-64/105 (60%) wo noted growth of new neurofibromas & 55/105 (52%) wo noted enlargement of existing neurofibromas during pregnancy; pregnancy induced hypertension (2%); preeclampsia (4%); HELLP (0,6%)	Preterm delivery 6%; IUGR 4%; PROM 2%; PPROM 3%; placental abruption 0,6%; placenta accreta 0,6%; postpartum hemorrhage 3%; CS 36%
Segal et al, 1999 ²⁸	Study of 13 pregnancies in 8 wo with NF1 in 3 yrs, matched with a control group (1:5)	8 wo, 13 pregnancies	Pts already diagnosed with NF1	Hypertension (12,5% vs. 4,6%)	Preterm delivery 30,8% vs.. 6,1%; IUGR 46,2% vs. 8,9%; stillbirth 23% vs. 1,5%; CS 38,5% vs. 7,7%; lower fetal weight 2379±940 vs. 3186±517
Isikoglu et al, 2002 ²⁹	a pregnant wo with a plexiform neurofibroma & its progress during & after pregnancy	1 case	Café-au-lait spots; multiple fibromas all over the body; axillary freckles; lisch nodules in R iris	Plexiform neurofibroma of R thigh which became smaller 10 mo after delivery (diameter of thigh from 105cm during pregnancy to 68cm). The pt claimed that the mass grew in all her past pregnancies, & shrunk somewhat after each delivery	Vacuum extraction for prolonged second stage

Study	Study purpose	Sample Size	Maternal manifestations	Maternal Complications	Fetal Complications
Posma et al, 2003 ³⁰	the development of malignant schwannoma during pregnancy in a pt with NF1	1 case	Typical neuro-cutaneous signs: multiple neurofibromas; café-au-lait spots; a 3-cm mass near the aortic arch (interpreted as a benign neurofibroma)	Thoracic pain; a 5-cm mass in the upper mediastinum (a large infiltrating mass in the foramina of the 3rd & 4th thoracic vertebrae without infiltration of the spinal cord); a malignant nerve sheath tumour grade III (not radically resected); photon radiotherapy; tumour-free for 3 yrs; 2nd pregnancy after ovulation induction; a short episode of sudden-onset thoracic & abdominal pain (subsided spontaneously) - in the postpartum period, severe abdominal pain recurred & became progressive (recurrent malignant schwannoma); the pt passed away 3 mo after delivery	Termination of the 1st pregnancy at 20 wks of gestation; delivery of the 2nd child at 40 wks of gestation
Kosec & Márton, 2006 ³¹	two cases of NF 1; previously known & detected during pregnancy respectively	2 cases	Café-au-lait spots; multiple fibromas all over the body; ophthalmologic lesions	Optic glioma	IUGR; preterm delivery by CS (1st case); termination of the pregnancy at 20 wks of gestation (2nd case)
Nelson et al, 2010 ³²	a pregnant wo with NF1 who presented respiratory symptoms at 11-12 wks due to a mediastinal sarcoma mass arisen by a neurofibroma	1 case	Pt already diagnosed with NF1	Newly diagnosed (11-12 wks) mediastinal neurofibroma with transformation to malignant peripheral nerve sheath tumor, confirmed after surgical excision; at 23 wks the pt developed acute respiratory symptoms as a recurrence of the sarcoma; the pt died as no therapeutic options where possible.	Due to extremely preterm pregnancy (23 wks) the family requested no obstetric interventions; pregnancy with no complications at the time of maternal death
Islam, 2012 ³³	A wo with NF1 & her pregnancy outcome	1 case	Café-au-lait spots; extensive cutaneous neurofibromas; multiple pelvic lesions (MRI); lesions within the spinal canal & foramina of all lower thoracic & lumbar vertebrae (MRI)	Aggravation of skin lesions	Labor induction at 40 wks due to aggravation of skin lesions with no problems

Study	Study purpose	Sample Size	Maternal manifestations	Maternal Complications	Fetal Complications
Terry et al, 2013 ¹³	To investigate whether vascular & other complications are more common in pregnant wo with NF1	1553 cases (identified among 19 million pregnancy-related admissions between 1988-2009)	Café-au-lait spots; multiple fibromas all over the body	Gestational hypertension; preeclampsia; cerebrovascular disease	IUGR; preterm labor by CS
Cecchi et al, 2013 ³⁴	a pregnant wo with NF1 & undiagnosed pheochromocytoma who died suddenly during CS due to acute hypotension	1 case	Café-au-lait spots; multiple fibromas	Cardiomyopathy by combination of PHEO & NF1 that presents with fatal acute severe hypotension, pulmonary edema & tachyarrhythmia following general anesthesia; maternal death	CS as a result of previous CS for breech presentation
Harshini et al, 2014 ³⁵	The pregnancy outcome of a wo with NF1	1 case	Neurofibromas all over the body; café-au-lait spots all over the body	none	none
Ramos-Zúñiga & Saldaña-Koppel, 2015 ³⁶	a progressive gradual increase in size & cystic transformation of a cervical neurofibroma during pregnancy, resected after delivery	1 case	Neurofibromas all over the body; café-au-lait spots all over the body	Cervical neurofibroma increasing in size; dysphagia, dysphonia, postural pain	none
Jain et al, 2015 ³⁷	increased rate of complications associated with pregnancy of 2 NF pts; diagnostic evaluation, management & dilemmas	2 cases	Pallor; icterus; multiple big & small fibromas all over the body; numerous large & small neurofibromas all over the body with a big plexiform mass hanging out from R eye	Generalized tonic-clonic seizure on 4th postpartum day due to a meningioma; cholelithiasis	Placenta previa grade III; severe oligohydramnios (AFI 3cm); preterm delivery by CS
Xiong et al, 2015 ³⁸	a pt with multiple neurofibromas beginning in the 3rd mo of her 1st pregnancy leading to diagnosis of NF1.		Dozens of new papules & nodules, progressively increasing in size & number; 3-10mm dark brown hyperpigmented papules & soft nodules located primarily on the back, chest, abdomen, arms; numerous 1-2mm hyperpigmented freckles on the trunk, face, & axillae; more than 6 café-au-lait macules larger than 1.5cm on the trunk; a dark brown hyperpigmented plaque on her R thigh (plexiform neurofibroma); mild scoliosis		
Dahiya et al, 2016 ³⁹	a case of NF in pregnancy, with transmission to the baby	1 case	Skin lesions all over the body	Vaginal bleeding	Placenta previa; delivery by CS; NF lesions on the newborn on the 3rd day of delivery

Study	Study purpose	Sample Size	Maternal manifestations	Maternal Complications	Fetal Complications
Remon-Ruiz et al, 2017 ⁴⁰	A pregnant wo with NF1 who developed hypertensive crises during 2nd trim (16 wks) that led to diagnosis of pheochromocytoma	1 case	Diagnosed with NF-1 during childhood	Mild hyperthyroidism in the 1st trimester; uncontrolled hypertensive crises (up to 170/105 mmHg) in 2nd trimester along with facial pallor, shaking hands & headache	History of 2 previous pregnancies: the 1st pregnancy ended in stillbirth at 31 wks due to placental abruption, the 2nd gave birth to a healthy 2500g female at 38 wks; Placental abruption with emergency CS at 35 wks at 3rd pregnancy; Adrenalectomy was performed at 23 wks
Leppävirta et al, 2017 ⁴¹	Retrospective register-based total population study in Finland, data comparison of pts with a confirmed diagnosis of NF1 with matched controls to examine pregnancies and deliveries;	176 NF1 wo with delivery between 1987-2013; 375 deliveries including 9 twin pregnancies (matched with 2.261 non-NF1 wo with delivery between 1987-2013)	Pts with a confirmed diagnosis of NF1 through register-based research	Increased risk for: hypertension; preeclampsia, maternal care for disproportion	Increased risk for: poor fetal growth; placental abruption; oligohydramnios; decreased gestational age at delivery, more significantly when mother & fetus were both affected by NF1; CS
Kalmantis et al, 2018 ⁴²	A wo with NF-1 & her pregnancy outcome	1 case	Neurofibromas all over the body (cutaneous & subcutaneous); café-au-lait spots all over the body; demyelination lesions of the brain & arteriovenous malformation of subarachnoid space of the cervical spine diagnosed 2 months prior to pregnancy	Neurofibromas & café-au-lait spots increased in number & size according to the pt	Placenta previa; delivery by CS at 36 wks due to spontaneous onset of labor
Well et al, 2020 ⁴³	to quantify growth of cutaneous & plexiform neurofibromas in NF1 pts during pregnancy, & to assess the onset of NF1 related symptoms	13 cases compared with 13 non-pregnant NF1 wo	Plexiform neurofibromas; cutaneous neurofibromas	No significant difference between groups; malignant transformation of PNF was not observed.	Not reported

CS: cesarean section; mo: month; NF: neurofibromatosis; pt: patient; spont: spontaneous; wo: woman/women

authors to have an increased risk of complications. Although information on pregnant women with NF1 is limited, the literature reports possible maternal disease aggravation as well as fetal/obstetric complications.

A short review of the literature is presented in Table 1.

Maternal complications reported, include increase of tumor burden, as a rise in number and size of tumors such as neurofibromas, café au lait spots, optic gliomas and malignant transformation of tumors [25,31,44,45]. Hypertensive complications, like gestational hypertension and preeclampsia as well as cerebrovascular complications are also of significant importance [11-14]. Cardiovascular disease of earlier onset and increased cardiac mortality seems to be the result of an incompletely understood effect of NF1 on the vascular system [46-48]. NF1 predisposes to pheochromocytoma and renal artery stenosis, both of which cause secondary hypertension of early onset [13]. A broad range of cerebrovascular abnormalities is also associated with NF1 including cerebral aneurysms [49] moyamoya syndrome [50] and ectatic or stenotic cerebral vessels [51] which may lead to stroke or cerebral hemorrhage predisposition. In the other hand fetal complications consist of spontaneous abortions of first trimester, stillbirth, intrauterine growth restriction, preterm labor by cesarean delivery, placenta previa, oligohydramnios [11,13,28,37,39,41]. All of these complications may be associated, at least in part, with the NF1-associated vasculopathy which is likely to determine a spectrum of disorders affecting trophoblast invasion and placental vascularity, thus causing abnormal placentation and resulting vasculopathy affecting the fetus [52-53]. Fetal distress, neurofibromatosis lesions on the newborn, malpresentations and cephalopelvic disproportion due to undiagnosed pelvic neurofibromas and pelvic bony contractures, as well as severe preeclampsia, abruptio placentae, pheochromocytoma, neurofibroma on spinal cord and elective repeat is reported to increase the rate of cesarean section in women affected by NF1 [11-13,41].

a. Effect of pregnancy on NF1

In most studies, an important percentage of patients, usually more than 50%, affected by NF1, during pregnancy, have reported an increase in terms of number and size of preexisting neurofibromas [11,54]. This growth tendency of neurofibromas, is suggested by in vitro studies, to be mediated mainly by estrogen, progester-

one and androgens along with epidermal growth factor, fibroblast growth factor and transforming growth factor alfa [8,9]. Subsequently to delivery, often patients who mentioned aggravation of the disease while pregnant, referred regression but no case of complete regression has been reported [29,54].

Since 1906 Brickner has described nodular lesions, that appear during pregnancy and gradually disappear after delivery [55]. Later Sharpe & Young (1937) and Moritz & Snider (1962) stated that pregnancy may provide a growth stimulus on neurofibromatosis skin lesions and that way promote diagnosis of the disease if it hasn't been established until then [44,45]. Swapp and Main on 1973 released an interesting study of 10 NF patients and their 24 pregnancies [25]. In five out of ten patients, the lesions of neurofibromatosis appeared for the first time during pregnancy. In the others the lesions increased in size and number. The lesions regressed considerably after delivery in seven of ten patients. Furthermore, they stated that hypertension during these pregnancies is more than a chance association possibly due to Neurofibromatosis vasculopathy. All ten patients to the end of their pregnancies have shown significant rise of mean blood pressure, while five of them were already hypertensive at first visit. Several case reports and studies of more patients have followed, to support that pregnancy might worsen NF1 disease tumor lesions or stimulate the rise of new ones or even provoke malignant transformation and emergence of pheochromocytoma. Recently Well et al. (2020) published a retrospective study that investigated the effect of pregnancy on tumor burden in 13 patients with NF1, matched with 13 non-pregnant patients as control group [43]. In this study, although some NF1 patients experienced a subjective increase of NF1-related clinical symptoms and tumor growth during pregnancy, growth of plexiform and cutaneous neurofibromas in pregnant patients, with MRI observation, was not significantly different compared to non-pregnant patients. Furthermore, no patient developed new plexiform neurofibroma (PNF) and no PNF underwent malignant transformation, which was expected given the small investigated patient group. The only noteworthy difference between the two groups was a significant growth of four singular neurofibromas during pregnancy compared to significant growth of only one neurofibroma in the control group. This might indicate that singular neurofibromas can actually be affected by pregnancy, which is in

accordance with previously described heterogeneous responses of tumor growth to hormone exposure in vitro [17,19,22] and case reports that presented significant growth of singular neurofibromas like Isikoglu et al. and Ramos-Zúñiga et al. [29,36].

b. Effect of NF1 on pregnancy

Maternal, fetal and obstetric complications have always been in the center of interest in pregnant women affected by neurofibromatosis. Many authors in the past have reported cases of women with NF1 that presented complications in one or more pregnancies. Subsequently most of the studies on larger patient samples as well as retrospective register-based analysis have confirmed that pregnancy complications are significantly increased among women with NF1.

Initially the results between some studies with more patients were contradictory. Hadi in 1995 reported, as a result of a study focused on 14 pregnancies of 8 women with NF1, a rate of live births as low as 50% [27]. This result attracted interest as previous similar studies like Jarvis and Crompton (1978) [26] and Weissman et al. (1993) [12] had published live birth rates that exceeded 90% (95.5% and 91.3% respectively). Also, Jarvis and Crompton [26] did not observe higher rates incidence of obstetrical complications in NF patients compared to the general population. Later, Dugoff & Sujansky (1996) [11] announced the results of a study based on questionnaire and medical records review of a total of 247 pregnancies of 105 women affected by NF1. In their study, although the rate of live birth was 74% and the rate of cesarean deliveries was increased, no increased risk for pregnancy complications was reported. A few years later Segal et al. (1999) [28] showed up with the evaluation on outcomes of 13 pregnancies on 8 patients with NF1, matched 1 to 5 with a control group. Interestingly, it has been documented a significant increase of the risk of all major obstetric

complications, mentioned before to relate with pregnancy in NF1. More precisely hypertension incidence in the study group was 12.5% versus 4.6% in the control group, preterm delivery 30.8% vs. 6.1%, IUGR 46.2% vs. 8.9%, Still-birth 23% vs. 1.5% and cesarean section 38.5% vs. 7.7% respectively. Additionally, it has been registered a lower fetal weight at delivery in women with NF1 (2379±940g vs. 3186±517g). To make things clearer new retrospective studies on larger patient sample have followed. In 2013 Terry et al. [13] conducted a population-based retrospective study including data from 1553 cases of pregnant patients with NF1 in USA which demonstrated significantly higher rate of gestational hypertension, preeclampsia, intrauterine growth restriction, cerebrovascular disease, preterm labor and cesarean delivery. Recently Leppävirta et al. (2017) [41] with their retrospective total Finnish population study, confirmed once more that in women with NF1, the risk for cesarean delivery and pregnancy complications, including hypertension, preeclampsia, poor fetal growth, placental abruption, maternal care for disproportion, and oligohydramnios, was significantly increased. In addition, it has been showed for the first time that the NF1 syndrome of the fetus might shorten even more pregnancy duration.

Conclusion

Summarizing, the latest literature agrees that pregnancy in patients with NF1 should be considered as at increased risk for obstetric complications. These patients need to be at close antenatal monitoring at tertiary centers for signs of hypertension/preeclampsia and intrauterine growth restriction that are considered to be responsible for stillbirths, preterm labor and higher rates of cesarean sections. Furthermore, close observation for signs of disease aggravation by clinicians, expert on neurofibromatosis, is also needed in order to guarantee the best possible outcome. ■

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