

Management and Outcome of Consecutive Pregnancies Complicated by Idiopathic Intracranial Hypertension

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ABSTRACT: **Background:** The effects of consecutive pregnancies on the course of idiopathic intracranial hypertension (IIH) are unclear in view of the scarce published data.

Objectives: To evaluate the course and management of visual and pregnancy outcomes of consecutive pregnancies with IIH.

Methods: The medical records of women with IIH in consecutive pregnancies were reviewed for neuro-ophthalmological findings, management, and visual and pregnancy outcomes.

Results: The study group comprised eight women with at least two consecutive pregnancies (mean age 27.3 ± 5.3 years). The mean duration of IIH prior to the first pregnancy was 3.4 ± 3.16 years. One woman with IIH pre-pregnancy symptoms and three women with clinical features of IIH during the second trimester of pregnancy (gestational week 21.7 ± 4.04) were treated with acetazolamide (250 mg every 8 hours). Symptoms resolved, resulting in uncomplicated first deliveries for all four. The first deliveries of four other women were by cesarean section due to obstetric indications. Only one woman developed symptoms and signs of IIH during her second pregnancy and was thus treated with acetazolamide. Two women who completed three pregnancies had no IIH symptoms during their pregnancies. The course and outcome of those pregnancies were normal.

Conclusions: IIH apparently does not worsen or even become symptomatic in consecutive pregnancies. The appropriate management of IIH in pregnant women is similar to management for non-pregnant women; neither the course nor the obstetric outcome of first and consecutive pregnancies is influenced by the presence of IIH.

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seen in women of childbearing age and is associated with recent weight gain or obesity, thus its prevalence changes from 19.3/100,000 in a high risk population to 0.8–1.7/100,000 in the general population.

The diagnosis of IIH is established using the modified Dandy criteria [2] following a meticulous search for other causes of raised intracranial pressure. Typical clinical features include headache, nausea, vomiting, papilledema, and transient visual obscurations and visual loss. Neuroimaging studies such as computed tomography and magnetic resonance imaging depict normal anatomy while the intracranial pressure measured by lumbar puncture is > 25 cmH₂O and the biochemical and cytological composition of the cerebrospinal fluid is normal.

The association between pregnancy and IIH is controversial, with a few studies mentioning pregnancy as a risk factor [3–5] and others that refute the etiologic relations between pregnancy and IIH [6]. The prevalence of IIH among pregnant women is reported to range from 2% to 12% [1]. Symptoms may become evident throughout gestation. The visual outcome is similar to that of non-pregnant IIH patients [1,6,7]. Given the limitations of performing neuroimaging studies in pregnant patients and the limited treatment availabilities, both the diagnosis and the management of these patients are determined on a case-by-case basis.

The hormonal milieu and the gestational physiologic alterations responsible for the symptomatic aggravation during pregnancy recur in repeated pregnancies among women with IIH. The effects of consecutive pregnancies on the course of the disease remain to be elucidated in view of the scarce published data. We sought to assess the course of IIH in repeated pregnancies.

PATIENTS AND METHODS

Included in this retrospective study were gravid patients with IIH diagnosed according to the modified Dandy criteria [Table 1] [3] and pregnant at least twice after the diagnosis had been made, during the period 2003–2008. All eligible women were seen in the neuro-ophthalmologic and high risk pregnancy outpatient clinics. Medical records from both clinics were reviewed for IIH symptoms, neuro-ophthalmologic findings, neuroimaging studies, IIH management, and visual and perinatal outcomes. This study was approved by the local institutional review board committee.

Idiopathic intracranial hypertension (or pseudotumor cerebri) is characterized by symptomatic increased intracranial pressure and papilledema in alert patients in the absence of an intracranial tumor. Neurological findings are unremarkable and miniscule (sixth nerve palsy) [1]. IIH is predominantly

IIH = idiopathic intracranial hypertension

Table 1. Modified Dandy criteria

Symptoms of raised intracranial pressure	Headache, nausea, vomiting, transient visual obscurations or papilloedema
No localizing signs	With the exception of abducens (CN VI) palsy
The patient is awake and alert	
Normal CT and MRI findings	With no evidence of cerebral thrombosis
Lumbar puncture opening pressure > 25 cmH ₂ O	With normal biochemical and cytological composition of the cerebrospinal fluid
No other explanation for raised intracranial pressure	

RESULTS

The medical records of eight women diagnosed with IIH who had at least two pregnancies after being diagnosed were retrieved. General and medical characteristics of the study group are shown in Table 2. The mean age at IIH diagnosis was 27.2 ± 5.3 years. The mean body mass index for the study group was 30.8 ± 5.6 (all in the obese range). Six were pregnant for the second time and two for the third time during the study period. Six women had been diagnosed with IIH prior to their first pregnancy. They had a mean IIH duration of 3.4 ± 3.16 years. No signs of hypertensive retinopathy were observed, even in those diagnosed with hypertension. Two women were diagnosed with IIH during pregnancy.

Prior to their first pregnancy, all eight women had best corrected visual acuity of 6/6 in both eyes. The presenting symptom of IIH in all women was headache and four also had transient visual obscurations. One had bilateral papilledema before pregnancy, and a visual fields test showed bilateral blind spot enlargement. She was treated with acetazolamide (acetazolamide is a carbonic anhydrase inhibitor that was found to decrease CSF production in humans at a dose of 250 mg three times daily). Treatment was discontinued postpartum along with complete resolution of symptoms. Only one of the eight women had symptoms of IIH during her second consecutive pregnancy after the diagnosis.

Overall, 4 of the 8 patients (50%) were treated with acetazolamide due to symptomatic exacerbation of IIH during their first post-diagnosis gestation. One woman, diagnosed with IIH prior to her first pregnancy (Case 1), had a BCVA of 6/7.5 and depression zones in both eyes on visual field testing. She was treated with acetazolamide (250 mg every 8 hours) with a gradual clinical improvement culminating in a full resolution of signs and symptoms in the immediate postpartum period. Three women (37.5%) complained of headaches followed by bilateral papilledema during pregnancy. One patient developed pre-gestational bilateral papilledema and was treated with acetazolamide throughout pregnancy, with cessation of treatment

CSF = cerebrospinal fluid
BCVA = best corrected visual acuity

Table 2. Characteristics of the studied patients at first diagnosis of IIH

Case	Age (yr)	Age at first episode (yr)	Past medical history	Medication	Total pregnancies	BMI	Duration of IIH prior to the first pregnancy
1	38	25	Hypothyroidism	Levothyroxine	2	31.25	8 yr
2	34	34	Hypertension, PCO	Omeprazole, methyldopa	2	29.7	NA*
3	30	25	Hypertension, hypothyroidism	Atenolol	2	43.57	3 yr
4	30	24	None	None	7	27.81	4 yr
5	38	34	None	None	2	33.75	2 yr
6	30	24.5	None	None	2	28.8	2 yr
7	32	20	None	None	2	26.17	8 yr
8	38	32	S/P BE Lasik 2002	None	4	25.97	NA*
Mean	33.7	27.2				30.8	

BMI = body mass index, IIH = idiopathic intracranial hypertension, PCO = polycystic ovarian syndrome, BE Lasik = laser-assisted in situ keratomileusis, NA* = not applicable: IIH was first diagnosed during pregnancy

Table 3. Results of visual testing of the eight study patients in their first pregnancy

Patient	Symptomatic	Visual acuity	Visual field	Fundus	Treatment
1	+	6/7.5	Depression zones L>R	Elevation+blurred margins R>L	Acetazolamide
2	+	6/6	Normal	Slight elevation, no NFL edema	Acetazolamide
3	-	6/6	Normal	Normal	None
4	-	6/6	Normal	Swollen disks	Acetazolamide
5	-	6/6	Normal	Normal	None
6	-	6/6	Normal	Normal	None
7	-	6/6	Normal	Normal	None
8	+	6/6	Nasal defects R>L	Swollen disks	Acetazolamide

L = left, R = right, NFL = nerve fiber layer

in the postpartum period after resolution of the symptoms. Two women, without pre-gestational diagnosis of IIH, were diagnosed during the second trimester (mean gestational age at diagnosis 23.5 ± 3.53 years). Headache and transient visual obscurations were reported in one patient during her first pregnancy. A neuro-ophthalmologic examination revealed bilateral papilledema. Visual fields test showed a normal right eye and a nasal defect on the left eye. She was treated with acetazolamide for one year and all symptoms eventually resolved. IIH was diagnosed in the second patient during her second pregnancy. She was also treated with acetazolamide and her symptoms resolved after delivery. The patients' visual acuity, visual field and fundus appearance during the first pregnancy are summarized in Table 3.

The average inter-pregnancy period for the study group was 34.9 ± 32.1 months (range 3–108 months). One patient

with symptomatic IIH during her first pregnancy had a relapse and was therefore treated with acetazolamide until full resolution of symptoms; she conceived 6 months later, 108 months after her previous delivery.

Symptoms of IIH during the consecutive post-diagnosis pregnancy were uncommonly reported. Only one woman (12.5%) developed headaches and transient visual obscurations with bilateral papilledema, BCVA of 6/6 for both eyes, and a normal visual field test. She was treated with acetazolamide 250 mg three times daily with rapid resolution of the optic disk edema. Notably, this patient was treated with acetazolamide for 5 months due to symptomatic IIH prior to her first pregnancy. Treatment was discontinued with the resolution of symptoms and signs. The course of the second pregnancy was uneventful ending with a vaginal delivery (Case 4). None of the remaining seven patients reported symptoms related to IIH in the course of their consecutive post-diagnosis pregnancy, and visual acuity was unchanged in all.

Four women delivered vaginally and four had a cesarean section. One patient had a placental abruption at 28 weeks, culminating in a vaginal delivery of a premature neonate weighing 1190 g who was later diagnosed with mild cerebral palsy. One woman with twins had a cesarean section at 31 weeks due to placental insufficiency after an asymptomatic pregnancy. Birth weights were 1425 g and 884 g, the latter affected with complications of prematurity. The mean gestational age for the second pregnancies was 36.1 ± 4.2 compared with 37.8 ± 0.6 weeks for the first (not statistically significant). The mean birth weight was 2511 ± 1109.7 g for the second pregnancy compared with 3059.8 ± 513.8 g for the first (not significant). All term neonates had Apgar scores of 9–10 at 5 minutes for both pregnancies while the three preterm neonates had scores of 6–7 at 5 minutes.

The course of a third post-diagnosis pregnancy was evaluated in two women. The time elapsed between the second and third pregnancies was 12 months for one woman and 19 months for the other. Neither had symptoms or signs of IIH during the third pregnancy and their BCVA and visual field tests remained normal. The gestational age was 38 and 38.5 weeks; mean birth weight was 3700 and 3500 g, and both neonates had Apgar scores of 9–10 at 5 minutes.

DISCUSSION

The pregnancy rate for IIH patients is similar to that of the general population [8]. IIH can occur during any trimester of pregnancy and the visual outcome is the same as for non-pregnant IIH patients [6]. Current reports suggest that pregnant IIH patients can be managed the same way as non-pregnant patients [9]. Increases in the rate of spontaneous abortion or fetal wastage have not been reported and were not seen in our patients. Therapeutic abortions to limit progression of visual loss were not indicated [6].

The literature contains single case reports and review articles demonstrating that pregnancy is a risk factor for IIH [3,4,10]. Digre and co-authors [8] observed that pregnancy occurs at the same frequency in normal patients and in those with IIH. The two major therapeutic goals in pregnant IIH patients are to preserve vision and to ameliorate symptoms, without sequelae, that could be harmful to the pregnancy. Most treatment regimens can be followed during pregnancy, but a significant caloric restriction is not recommended. Dietary control must ensure that ketosis is avoided [1,2,9].

Glucocorticoids, carbonic-anhydrase inhibitors (acetazolamide), diuretics, and serial lumbar punctures have been used to lower intracranial pressure both in pregnant and non-pregnant women [8,11]. Lumbar puncture can be performed safely without fear of brainstem herniation [12]. Therapy may be initiated for 1 to 2 weeks with serial lumbar punctures, or acetazolamide.

Acetazolamide is the mainstay of medical therapy for IIH. It is classified as class C according to the Food and Drug Administration. This drug had previously been considered the preferred therapy after 20 weeks of gestation, since sacrococcygeal teratoma had been reported with earlier use [8]. A recent report of 12 women treated with acetazolamide for IIH during pregnancy showed no adverse pregnancy outcomes in terms of fetal loss or congenital malformation. Acetazolamide at high doses may produce birth defects in animals; however, there is little clinical or experimental evidence to support any adverse effect of the drug on pregnancy outcomes in humans. If the clinical situation mandates the use of acetazolamide in IIH, then the drug can probably be offered after appropriate informed consent [13].

Management of labor and indications for cesarean delivery for patients with IIH has been controversial [14,15]. Normal labor may be allowed, with cesarean delivery reserved for obstetric indications. Adequate labor analgesia is recommended for vaginal deliveries since uterine contractions are associated with increased CSF pressure more marked during periods of inadequate analgesia [5]. In a recent report concerning anesthetic considerations in IIH patients, the authors concluded that despite the presence of raised intracranial pressure in these patients, there are no specific contraindications to neuraxial techniques, and uncal herniation has not been reported to occur in patients with IIH [16].

Few publications report the outcome of subsequent pregnancies in women with IIH [17]. This is the first report of multigravid women with IIH. We reviewed eight such cases and evaluated the course of their disease as well as the course of their first and successive pregnancies. Only three (37.5%) had IIH symptoms during their first pregnancy. Subsequent treatment with acetazolamide led to resolution of symptoms. Only one patient (12.5%) had active IIH during the second pregnancy and was treated with acetazolamide. The two women

(12.5%) in our study who were pregnant for a third time were free of symptoms and signs of IIH. None of the pregnant women who were and are still being followed in our clinic lost their vision due to IIH. All have BCVA of 6/6, and none needed a lumbar puncture shunt or optic nerve sheath fenestration. Three of the eight patients had concurrent hypothyroidism. In the literature only a few cases of hypothyroidism have been reported to develop IIH [18] and there are few reports of presumed levothyroxine-induced pseudotumor cerebri (IIH) in patients being treated for hypothyroidism [19,20].

IIH treatment is aimed at alleviating pain and preventing visual loss in pregnant women since severe loss of vision may reportedly develop in 10% of pregnant women with IIH [1]. Management should be the same for pregnant as for non-pregnant patients [8]. It is well established that one pregnancy does not influence the course of the disease. The findings of our current study also indicate that consecutive pregnancies have no effect (positive or negative) on the course of IIH and that IIH does not influence the course of consecutive pregnancies. Management of the pregnancies is therefore dictated entirely by obstetric indications.

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Capsule

Plasma cells require autophagy for sustainable immunoglobulin production

The role of autophagy in plasma cells is unknown. Pengo et al. found notable autophagic activity in both differentiating and long-lived plasma cells and investigated its function through the use of mice with conditional deficiency in the essential autophagic molecule Atg5 in B cells. Atg5^{-/-} differentiating plasma cells had a larger endoplasmic reticulum (ER) and more ER stress signaling than did their wild-type counterparts, which led to higher expression of the transcriptional repressor Blimp-1 and immunoglobulins and more antibody secretion. The enhanced immunoglobulin synthesis was associated with less intracellular ATP and more death of mutant plasma cells, which identified an

unsuspected autophagy-dependent cytoprotective trade-off between immunoglobulin synthesis and viability. In vivo, mice with conditional deficiency in Atg5 in B cells had defective antibody responses, complete selection in the bone marrow for plasma cells that escaped Atg5 deletion, and fewer antigen-specific long-lived bone marrow plasma cells than did wild-type mice, despite having normal germinal center responses. Thus, autophagy is specifically required for plasma cell homeostasis and long-lived humoral immunity.

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