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Reproductive implications of endoscopic third ventriculostomy for the treatment of hydrocephalus☆

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Abstract

Objective: The objective of this study was to compare reproductive function after two neurosurgical procedures for treating non-neoplastic hydrocephalus; endoscopic third ventriculostomy (ETV) and ventriculo-peritoneal shunt (VP).
Study design: A cohort of 96 women who underwent neurosurgical procedures to treat non-neoplastic hydrocephalus at the Cleveland Clinic between January 1995 and January 2004 was identified. A follow up mailed survey was sent to all identified women between 15 and 45 years of age. In addition, phone interviews were performed to complete the required data. Clinical, laboratory and operative details were collected from 69 participants.
Results: There was a two-fold significant increase in the menstrual irregularities after the procedure in the ETV group [5/52(10%)–10/52(19%), $P = 0.03$] while those treated with VP shunt maintained the same menstrual pattern postoperatively. The rate of pregnancy was higher in the VP group compared to the ETV group, but did not reach statistical significance [8/17(47%) vs. 17/52(33%), $P = 0.462$]. Similarly, the rate of term pregnancies was higher in the VP group compared to ETV group [8/8(100%) vs. 13/17(76%), $P = 0.269$], which reflected a higher spontaneous miscarriage rate in ETV compared to VP group [4/17(33%) vs. 0/8(0%), $P = 0.269$].
Conclusion: ETV appears to alter reproductive function postoperatively. In patients who establish a pregnancy, abortion rates seem to be higher in the ETV group; however, a prospective study will be required to validate these observations.

Keywords: Hydrocephalus; Reproduction; Endoscopic third ventriculostomy

1. Introduction

The modern practice of shunting the cerebrospinal fluid (CSF) in hydrocephalic patients to relieve the increased intraventricular pressure has increased their long term survival [1,2]. This longer survival resulted in new challenges to improve the quality of life of those young adults including issues related to potential fertility and menstrual disorders. The increase in the intracranial pressure in patients with chronic hydrocephalus is commonly associated with dysfunction in the hypothalamic pituitary ovarian axis [3]. This dysfunction can result in precocious puberty, delayed puberty, and primary or even secondary amenorrhea [4,5].

In those patients, luteinizing hormone (LH) and follicle-stimulating hormone (FSH) serum levels were reported to be lower than normal [3,6]. In addition, administration of a gonadotropin releasing hormone (GnRH) agonist resulted in elevation of the LH and FSH levels, indicating the integrity

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of the pituitary part of the hypothalamo-pituitary ovarian axis and suggesting a hypothalamic disorder [7]. To date, the most appealing explanation for this observed dysfunction is the effect of compressive force on different areas of hypothalamus that are next to the third ventricle [3]. The neurons at the base of the third ventricle are the GnRH neurons that run from their respective nuclei to the median eminence. This compressive force hinders the pulsatile release of GnRH from its cell bodies located anterior and posterolateral to the third ventricle [8]. This effect may be just a functional disturbance secondary to compression or may cause focal or global ischemia that leads to axonal injury and decelerated neuronal transmission through the floor of the third ventricle and the pituitary stalk [9]. On the other hand, in the case of precocious puberty compressive force may cause disruption of the inhibitory fibers (endogenous opioids and dopamine) that can in turn lead to removal of chronic inhibition and premature stimulation of GnRH pulse generator, resulting in precocious puberty [5].

In most cases, the primary pathology which resulted in the increase in intracranial tension is the main cause for reproductive dysfunction; however, in some cases shunt procedures themselves might be a contributory factor especially when the observed dysfunction started after the shunt procedure [10,11]. The standard operation usually performed for treating such cases is a ventriculo-peritoneal shunt (VP) which is an open surgical procedure that entails diverting the cerebrospinal fluid from the dilated ventricles to the peritoneal cavity. Another more recent procedure is the endoscopic third ventriculostomy (ETV) [12]. It entails creating a shunt between the floor of the third ventricle and the cisterna magna [13]. This minimally invasive shunting procedure has gained popularity as an effective treatment for hydrocephalus [14]. Endoscopic third ventriculostomy causes dramatic improvement in the cognitive functions in all patients treated by this procedure [15]. Whether a similar improvement in reproductive functions will occur after this operation is unclear. Improvements in the menstrual pattern and endocrine profile after ETV have been reported in two case reports [16,17], but to the best of our knowledge, no comprehensive studies have addressed this issue.

The objectives of the current study were to report on the reproductive functions in treated hydrocephalic females and to compare the effect of ETV and VP shunt on various aspects of women's reproductive functions.

2. Material and methods

This study was approved by the Institutional Review Board of The Cleveland Clinic Foundation. All the records of female patients who were diagnosed with hydrocephalus during the period from January 1995 to January 2004 were reviewed. Patients were considered for inclusion in this study if they were between 15 and 45 years old, had body mass index between 19 and 30 kg/m^2, were diagnosed with hydrocephalus due to non-neoplastic causes, were surgically treated with either ETV or VP shunt, and were not diagnosed with endocrine abnormalities before surgery including thyroid, adrenal abnormalities or diabetes mellitus.

2.1. Study questionnaire

A self-administered questionnaire was prepared by the study investigators and piloted in a small group of women during their follow-up visits. Ninety-six study participants were identified from the hospital records of The Cleveland Clinic Foundation. All the eligible participants were contacted by mail. The posted package contained the patient information sheet, a consent form for retrieving hospital-notes, the questionnaire, an invitation to attend a phone interview, and a postage-paid reply envelope. Reminder study packages were sent to all patients who had not responded within 3 months. Phone interviews were performed by a trained research nurse to complete the required data only in patients who accepted the invitation sent to them by mail.

2.2. Study population and data collection

Out of the 96 patients included in this study, 27 were subsequently excluded for a variety of reasons. Five patients were excluded because they had total abdominal hysterectomy and bilateral salpingoophrectomy due to severe endometriosis and fibroids. Five more patients were excluded because they were on continuous combined oral contraceptive pills. In addition, 2 more patients were excluded because they had bilateral tubal ligation and ovarian cysts. We were not able to contact 10 patients and 5 of the identified patients declined participation in the study. The data from the remaining 69 patients with completed questionnaires and phone interviews were subsequently extracted. Collected data included information regarding clinical history, menstrual history, obstetrics history, mode of presentation, results of all investigations, results of clinical examination, type of surgery and postoperative follow up.

2.3. Statistical analysis

Comparisons between the 2 groups were performed using independent sample t-test and Mann Whitney test according to the distribution of individual continuous variables. Chi-square and Fisher exact tests were used for comparisons between categorical variables, accordingly. For the change from baseline in each group, paired t-test or Wilcoxon Sign Rank tests were used for continuous variables while McNemar test was used for categorical variables. The primary endpoint of the analysis was the proportion of menstrual dysfunction in the 2 study groups after the procedure. Using a 2-tailed chi-square test with an α error of 0.05, 69 subjects in 2 unequal groups (52 and 17) provided 90% power to detect a difference of 35% (i.e. 5% vs. 40%)

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Table 1
Clinical characteristics of the endoscopic third ventriculostomy group compared to the ventriculo-peritoneal shunt group of the study population[a]

	ETV ($n = 52$)	VP shunt ($n = 17$)	p-value
Age at procedure	32 (23, 39.5)	33 (23.5, 41.5)	0.736
Age at menarche	12 (10.5, 13)	12 (12,14)	0.307
Weight (kg)	71.2 ± 21.7	69.6 ± 17.9	0.196
Height (m)	1.6 ± 0.4	1.6 ± 0.3	0.202
BMI (kg/m^2)	25 ± 5.7	27 ± 3.6	0.095
Type of hydrocephalus			
Aqueductal stenosis, n (%)	46/52 (88.5%)	15/17 (88.3%)	0.980
Congenital hydrocephalus, n (%)	6/52 (11.5%)	2/27 (11.7%)	
Duration from the first intervention (years)	5.5 ± 10.3	1.2 ± 0.5	0.005
Number of previous shunt, n	27/52 (52%)	17/17 (100%)	0.001
One previous shunt, n	7/27	6/17	0.521
>1 previous shunt, n	20/27	11/17	

ETV, endoscopic third ventriculostomy; VP, ventriculo-peritoneal shunt.
[a] Mean and standard deviation were used for continuous variable with normal distribution while median and interquartile range (25th and 75th percentile) were used for continuous variables if the distribution was skewed. Comparisons were done using independent t-test or Mann Whitney test for continuous variables and χ^2 tests or Fisher exact test for categorical variables.

(nQuery Advisor, version 4.0, Statistical Solutions, Saugus, MA, United States). Statistical significance was considered at $P < 0.05$. Data were analyzed using the SPSS version 13 (SPSS Inc., Chicago, IL, United States).

3. Results

3.1. Demographic variables

Complete data were available for 69 treated hydrocephalic women; 52 patients (75.4%) were treated by ETV and 17 patients (24.6%) were treated by VP shunt. The median age in the ETV group was 32 years (interquartile range (IQR), 23–39.5 years) compared to 33 years (IQR, 23.5–41.5 years) in the VP shunt group Mann Whitney test, $P = 0.736$. The age at menarche was 12 years (IQR, 10.5–13 years) in the ETV group compared to 12 years (IQR, 12–14 years) in the VP group, Mann Whitney test, $P = 0.307$). Similarly, there was no statistically significant difference regarding the BMI (25 ± 5.7 kg/m^2 compared to 27 ± 3.6 kg/m^2, $P = 0.095$) between the 2 groups. Other clinical data are reported in Table 1.

3.2. Menstrual patterns and subsequent fertility

There was a two-fold increase in menstrual irregularities after the procedure in the ETV group [5/52(10%)–10/

Table 2
Menstrual and pregnancy endpoints in the endoscopic third ventriculostomy group compared to the ventriculo-peritoneal third shunt group

	ETV ($n = 52$)			VP shunt ($n = 17$)		
	Preoperative	Postoperative	p-value[a]	Preoperative	Postoperative	p-value[a]
Menstrual functions						
Period (days)	4.60 + 1.1	4.75 ± 1.4	0.225	4.35 + 2.7	4.41 + 2.6	0.332
Rhythm♣						
Normal	44 (85%)	39 (75%)	0.030	17 (100%)	17 (100%)	>0.99
Irregular	5 (10%)	10 (19%)		0 (0%)	0 (0%)	
Secondary amenorrhea	3 (5%)	3 (6%)		0 (0%)	0 (0%)	
Flow						
Normal♠	47 (90%)	47 (90%)	>0.99	13 (76%)	13 (76%)	>0.99
Light	1 (2%)	1 (2%)		2 (12%)	2 (12%)	
Heavy	4 (8%)	4 (8%)		2 (12%)	2 (12%)	
Total pregnancies[#]	–	17/52 (33%)	NA	–	8/17 (47%)	NA
Term pregnancies[##]	–	13/17 (76%)	NA	–	8/8 (100%)	NA
Spontaneous miscarriages[##]	–	4/17 (24%)	NA	–	0/8 (0%)	NA

ETV, endoscopic third ventriculostomy; VP, ventriculo-peritoneal; NA, not applicable.
[a] Comparisons were based on the change from baseline preoperative levels or proportions using paired t-test or Mann Whitney test for continuous variables and χ^2 tests or Fisher exact test for categorical variables.
♣ Normal rhythm is defined as having menstrual periods at regular 28–35 days interval.
♠ Normal flow was evaluated subjectively.
[#] χ^2 test for comparison between the proportions of women who had spontaneous pregnancy after the procedure in the 2 groups ($P = 0.462$).
[##] Fisher exact test for comparison of pregnancy outcome in the 2 groups ($P = 0.269$).

52(19%), $P = 0.03$] while those treated with VP shunt maintained the same menstrual pattern postoperatively. This change in pattern was not associated with change in the flow (Table 2).

The rate of pregnancy was higher in the VP group compared to the ETV group, but did not reach statistical significance [8/17(47%) vs. 17/52(33%), $P = 0.462$). The course of all pregnancies maintained until term was uneventful. All ended up with spontaneous vaginal deliveries of healthy children without birth defects. Spontaneous miscarriages were observed only in the ETV group where 4 (33%) cases of spontaneous abortion were reported during the follow up period (Table 2).

There were 4 patients in the ETV group that had elevated prolactin level (>20 ng/mL) postoperatively. The mean postoperative prolactin level in those 4 patients was 32.6 ± 2.9 ng/mL compared to a preoperative level of 17.2 ± 3.2 ng/mL. The difference was not statistically significant ($P = 0.08$).

4. Discussion

Endoscopic third ventriculostomy is a neurosurgical procedure in which a perforation is made to connect the third ventricle to the subarachnoid space as an alternative to shunt revision. The telescope is inserted in the floor of the third ventricle. The created fenestration will be subsequently dilated by inflatable balloon to the desired diameter (Fig. 1). The fenestration site is meant to be midway between the two mamillary bodies and the infundibular recess (Fig. 2A and B). The infundibular recess is exactly where the pituitary stalk begins with all the fibers conveying hypothalamic factors that control the secretions of the anterior pituitary gland including GnRH.

The beneficial role of ETV in improving the cognitive functions in the treated patients has been previously reported [15]. However, there were conflicting data regarding the

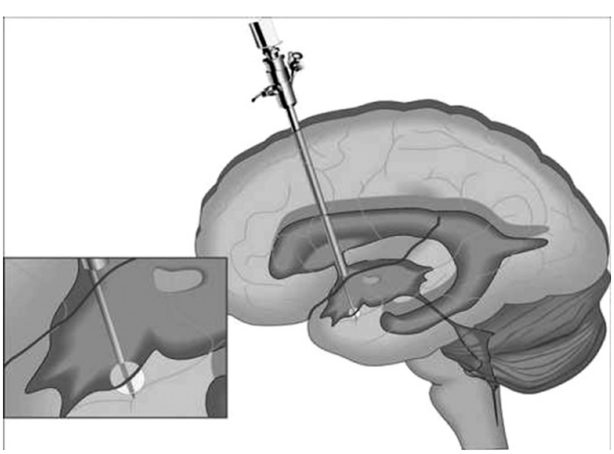

Fig. 1. Drawing showing a sagittal view of the third ventricle with the endoscope. The caption to the left is a magnified version for the view of the inflatable balloon used to dilate the fenestration.

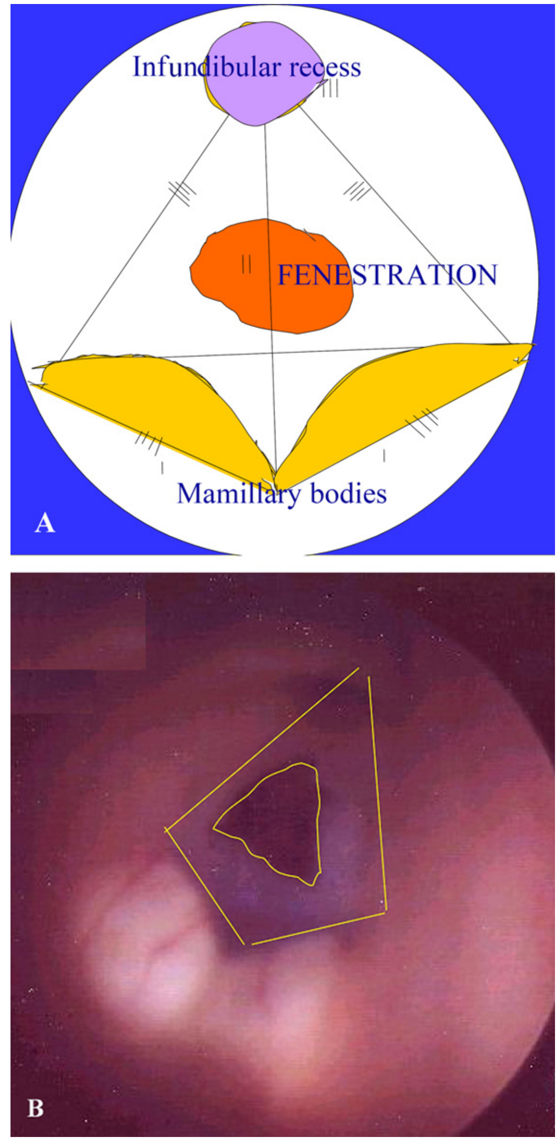

Fig. 2. Endoscopically identified anatomy at the floor of the ventricle (A) illustration and (B) endoscopic view.

menstrual patterns and the subsequent reproductive functions in those patients after surgery. Previous case report published by Touraine et al. showed improvement in the menstrual patterns, LH level and gonadotropin pulses after ETV [16]. On the contrary, examining the endocrine profile of 20 children who underwent ETV showed at least one abnormal value in TSH, T3, T4, cortisol, ACTH and prolactin in each of the examined children [18].

The present study showed a trend towards having more irregular menstrual cycles after ETV and not VP shunt after surgery. This difference in the results of ETV may be due to the possibility of a hydrocephalic-induced disturbance in the anatomy of the floor of the third ventricle previously reported in cases of chronic hydrocephalus [19]. This anatomical disturbance may lead to accidental injury in the endocrine nuclei or their fibers during the endoscopic procedure. In this study we observed a two-fold increase in

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the prolactin level after ETV which was consistent with previous reports [18]. However, this rise was not statistically significant. This could be a sample size problem in our study due to the fact that pre and postoperative prolactin values were available only in 4 patients. This increase in the level of prolactin provides some explanation for the higher rate of menstrual irregularities observed in ETV group. This hypothesis is supported by the fact that the arcuate nucleus which secretes dopamine (prolactin inhibitory factor) is located in the most ventral part of the third ventricle. The small cells of this nucleus are in close contact with the ependymal lining of the third ventricle. Consequently, inadvertent injury during endoscopic surgery may disrupt part of this nucleus.

These findings could also be explained by two important observations regarding the surgical anatomy of the third ventricle in hydrocephalic patients. First, ETV is usually performed for obstructive hydrocephalus which is usually associated with more extreme expansion of the third ventricle which could bring the nuclei or their fibers closer to the dilated ventricle. Second, third ventricular size reduction is much less after ETV compared to VP shunt, consequently even after surgery the third ventricle is still dilated after ETV. The present study did not show any significant difference in the mean duration of the menstrual period or the amount of flow before and after the surgery in both groups or between groups.

A review of 138 pregnancies after a VP shunt procedure in USA showed a primary favorable outcome with only 5 cases of preterm labour, one still birth, 32 miscarriages and 4 induced abortions [20]. However, these results do not include risks of pregnancy in these females like obstruction of VP shunt and risks of invasive procedures such as epidural and spinal anaesthesia [1,21]. On the other hand, there were no reports on pregnancy after ETV. The current study showed better pregnancy outcome after VP compared to ETV shunt with more term deliveries and fewer miscarriages in the VP group compared to the ETV group. However, we cannot be certain whether the difference in reproductive performance between the 2 groups was due to different underlying pathology or due to the type of the procedure itself.

One important limitation of the current study is the small sample size. Another limitation is the absence of randomization which controls for unknown confounders and provides more valid results. However, a randomized clinical trial would be difficult and expensive due to the long follow up needed. With the increasing success of shunt operations, more numbers of those young women are expected to reach childbearing period. A multicenter prospective registry including those young women would be a plausible alternative and would provide more cases and valid and reliable data.

In conclusion, ETV is causing significantly more alteration in the rhythm of the menstrual cycle after surgery in comparison with VP shunt and this alteration may be attributed to changes in prolactin hormone level. In addition, pregnancy after ETV is associated with less favorable outcome compared to VP shunt. A closer look into the hormonal alterations and the reproductive functions after ETV in a more comprehensive study with a long-term follow up is needed.

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