

# The Role of Indomethacin in Isolated Polyhydramnios

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## ABSTRACT

**Objective:** To study the role of Indomethacin in patients with Idiopathic Polyhydramnios who were symptomatic.

**Methods:** A prospective study was conducted in Prathima Institute of Medical Sciences, Karimnagar from September 2017 to May 2019. Eighteen patients with Idiopathic Polyhydramnios who presented with respiratory embarrassment, premature opening of os or presence of uterine activity were given Indomethacin orally at a dose of 25mg 6th hourly. The significance of changes in AFI was tested by paired t test.

**Results :** There was significant improvement in the symptoms in all the eighteen patients. The mean age of the patients in our study was 26.4±5.5 years. The majority 14(77.7%) of women were multigravida. Mean gestational age at presentation was 30.78±1.56 weeks. Mean AFI at presentation was 31.56±3.68 cm. Indomethacin was given orally at a dose of 25mg, every 6th hourly for a mean duration of 22.5±6.38 days. Mean AFI at the end of treatment was 20.28±5.64 cm. Pregnancy was prolonged by an average of 5.5±1.89 weeks. The difference in AFI at the end of treatment was statistically significant (p<0.05). Oligohydramnios was seen in one patient. Mean gestational age at delivery was 36.28±1.41 weeks. 17(94.4%) of them had good neonatal outcome. There was one neonatal death at < 7 days of birth.

**Conclusion:** Indomethacin significantly decreases amniotic fluid volume in patients with Idiopathic Polyhydramnios and relieves symptoms but close surveillance is necessary.

**Keywords:** Isolated Polyhydramnios , Indomethacin, AFI

## Introduction

Amniotic fluid surrounds the fetus during the intrauterine development. The fetus maintains its amniotic fluid volume within a normal range throughout the pregnancy. Factors controlling amniotic fluid volume are poorly understood, fetal urination is believed to be the major source of amniotic fluid.<sup>1</sup> The fetal respiratory system, gastrointestinal tract, umbilical cord and fetal surfaces of placenta are additional sources of amniotic fluid production.<sup>2</sup> Whenever there is a disturbance in the mechanism of production, fetal resorption and secretion of amniotic fluid, polyhydramnios occurs. Polyhydramnios is defined as an abnormally increased amniotic fluid volume of >2000ml or Amniotic Fluid Index of  $\geq 24$  cm or more than 95<sup>th</sup> percentile for gestational age.

Polyhydramnios is categorized as mild if AFI is 24 to 29.9cm; moderate if AFI is 30 to 34.9cm and severe if AFI  $\geq 35$ cm. The overall incidence of polyhydramnios is 1-2%. Maternal disorders like Diabetes, TORCH infections, drug usage, and fetal conditions like congenital and chromosomal abnormalities, Rh isoimmunisation , multiple gestations and placental abnormalities like chorioangioma are associated with polyhydramnios. However in 70% of the cases of polyhydramnios the cause is not known and it is referred as Idiopathic Polyhydramnios.<sup>3</sup>

Polyhydramnios is associated with increased perinatal morbidity and mortality.<sup>4</sup> It is associated with maternal complications like respiratory difficulties resulting from pressure of amniotic fluid on the diaphragm, abnormal presentation, premature uterine contractions leading to PROM and premature birth, abruptio placentae due to sudden decompression of uterus. Treatment in polyhydramnios is indicated only when symptoms like respiratory embarrassment, excessive uterine activity or premature opening of os occurs. Symptomatic patients may be treated with amniocentesis. However it is an invasive procedure with risk of preterm labour, recurrence, infections and abruptio placentae.<sup>5</sup> Medical management of polyhydramnios is the use of Indomethacin which was first reported by Cabrol.<sup>6</sup> The aim of our study is to observe the role of Indomethacin in symptomatic cases of Idiopathic Polyhydramnios.

## Materials and Methods:

The present study was a prospective and analytical study conducted in Prathima Institute of Medical Sciences during the period from September 2017 to May 2019. Eighteen pregnant women with Idiopathic Polyhydramnios who presented with symptoms such as respiratory difficulties, premature opening of os or presence of uterine activity were included in the study.

Ultrasound was done to determine Amniotic Fluid Index. An AFI of  $\geq 24$ cm using the four quadrant technique was considered as Polyhydramnios. It was classified as mild when AFI was 24 to 29.9 cm, moderate when AFI was 30 to 35 cm and severe when AFI was  $>35$  cm. Level II ultrasound was done to detect the presence of any congenital anomalies of the fetus, hydrops, multiple gestation and the presence of any placental anomalies . Patients with any of these conditions were excluded from the study.

Indomethacin was administered orally at a dose of 25mg, every 6th hourly. The drug was stopped when there was a decrease in the AFI and the patient was symptom free or if any complications like oligohydramnios, fetal distress or gastritis occurred. The patient was admitted to the hospital for close monitoring. Baseline investigations such as CBP, RFT, electrolytes were done and repeated twice weekly. AFI was measured twice a week and fetal 2DECHO was done before the start of the treatment and then every week to look for premature closure of fetal ductus arteriosus. After birth neonate was investigated by 2DECHO, RFT and ultrasound for any abnormalities. Neonates were followed for every month till six months of age. Metric data were described as mean  $\pm$  SD. Significance was checked with paired t test by IBM SPSS Statistics (Version 22). p value of  $< 0.05$  was considered significant.

#### Result:

There were a total of 4900 cases of which 72 were cases of polyhydramnios. Incidence being 1.47%. Among the 72 cases of polyhydramnios, 51(70%) cases were due to Idiopathic Polyhydramnios, 11(15.2%) were due to diabetes and 10(13.8%) cases were due to congenital anomalies and infections.

Of the 51 cases of Idiopathic Polyhydramnios, 18 cases were symptomatic and were treated with Indomethacin. When demographic characteristics were taken into consideration, the mean age of presentation was  $26.4 \pm 5.5$  years. 55.5% of them belonged to an age more than 25years. 77.7% were multigravida. A total of 8(44.4%) women belonged to low socioeconomic status.( Table 1)

**Table 1** Demographic characteristics of the patients

Characteristics		No of Cases n =18	%
1. Age	<20	2	11.11
	20-25	6	33.33
	25-30	8	44.44
	>30	2	11.11
2. Parity	Primi	4	22.22
	Multigravida	14	77.77
3.Socioeconomic status	Lower	8	44.44
	Middle	6	33.33
	Upper	4	22.22
4.Gestational age at presentation (weeks)	Mean	$30.78 \pm 1.56$	

Of the 18 cases, 6(33.3%) presented with mild, 9(50%) with moderate while 3(16.6%) presented with severe polyhydramnios. In our study polyhydramnios was diagnosed between 28 and 34 weeks. Mean gestational age observed was  $30.78 \pm 1.56$  weeks. After treatment with Indomethacin, there was symptomatic relief in all patients. There was a significant decrease in AFI in all cases.

The mean AFI at presentation was  $31.56 \pm 3.68$  cm. The mean

AFI at the end of treatment was  $20.28 \pm 5.64$  cm. Mean decrease in AFI was by  $11.28 \pm 5.04$  cm. There was statistically significant reduction in amniotic fluid volume following indomethacin therapy, the p value being  $< 0.05$  which is statistically significant. Average duration of therapy in our study was  $22.5 \pm 6.38$  days. Mean time of prolongation of pregnancy was by  $5.5 \pm 1.89$  weeks. (Table 2)

Table-2 AFI after indomethacin therapy

INDOMETHACIN THERAPY					
S.No.	AFI at Presentation (cm)	AFI at the end of Treatment (cm)	Duration of Treatment (days)	Pregnancy prolonged (weeks)	Decrease in AFI (cm)
1	29	18	28	7	11
2	32	23	28	6	9
3	33	18	30	9	15
4	34	22	21	8	12
5	28	15	30	7	13
6	27	16	21	5	11
7	28	19	14	5	9
8	27	20	28	8	7
9	34	20	14	4	14
10	40	30	30	6	10
11	32	3	21	3	29
12	35	25	14	5	10
13	34	26	28	6	8
14	31	21	21	5	10
15	32	22	14	3	10
16	36	24	21	4	12
17	30	23	28	6	7
18	26	20	14	2	6
Mean	31.56	20.28	22.50	5.50	11.28
SD	3.68	5.64	6.38	1.89	5.04

Of the 18 patients, 11(61%) delivered after 37 weeks, and in 6(33%) pregnancy could be carried forward to 34 to 36 weeks.

Mean gestational age at delivery was 36.28±1.41 weeks. (Table 3)

Table-3 Neonatal outcome

Gestational age at delivery	No. of cases n = 18	%	Neonatal Outcome
<34 weeks	1	5.5%	Neonatal death <7days
34-36 weeks	6	33.3%	Live birth
>37 weeks	11	61.1%	Live birth

One patient who was discharged continued taking Indomethacin at home without our advice and without any surveillance, returned with severe oligohydramnios.

The patient underwent emergency LSCS at 33 weeks for fetal distress. But the neonate died at < 7days. The remaining 17 patients had good neonatal outcomes. There were no maternal complications in all the 18 patients following treatment with Indomethacin.

#### Discussion:

Indomethacin is a nonsteroidal anti-inflammatory drug. It causes reversible inhibition of cyclooxygenase enzyme which inhibits the production of prostaglandins.<sup>7</sup> Indomethacin readily crosses the placenta and can decrease the production of amniotic fluid by increasing the absorption of fluid by lungs, reducing the urine output by reducing renal blood flow and increasing the renal vascular resistance. It also causes an increase in fetal secretion of antidiuretic hormone which further decreases the urine output.<sup>8,9</sup> The reported incidence of polyhydramnios varies between 0.4 and 3.3%.<sup>4,10</sup> In our study incidence observed was 1.47% which is similar to the study conducted by Shrestha A et al.<sup>11</sup>

In our study Idiopathic Polyhydramnios accounted for 70% of the cases which was similar to a study conducted by Pri-Paz et al and Sandlin AT et al.<sup>4,12</sup> Wiegand SL et al reported that most of the cases (78%) belonged to mild polyhydramnios and about 21% of cases were moderate to severe polyhydramnios.<sup>13</sup> But in our study as 18 cases of Idiopathic Polyhydramnios with symptoms were included, 6 cases (33.33%) belonged to mild and 12 cases (66.66%) belonged to moderate to severe polyhydramnios.

In our study most of the women belonged to the >25 years age group, and majority 14 (77.7%) were multigravida, similar to the study conducted by Tariq S et al.<sup>14</sup>

Lallar et al reported that most of the cases were diagnosed between 28 and 36 weeks of pregnancy.<sup>15</sup> In our study polyhydramnios was diagnosed between 28 and 34 weeks of gestation. Mean gestational age at presentation in our study was 30.78±1.56 weeks similar to study by Abhyankar et al and Carmona F et al.<sup>16,17</sup>

In our study there was a significant decrease in amniotic fluid when given in patients with Idiopathic Polyhydramnios similar to study conducted by Abhyankar et al, Abou-Ghannam G et al and Block Abraham Dana et al.<sup>16,18,19</sup> Pregnancy was prolonged by an average of 5.5±1.89 weeks and average duration of therapy was 22.5±6.38 days. These findings were similar to study conducted by Shrestha A et al and Abhyankar et al.<sup>11,16</sup>

Kirshon et al and Mamopoulos et al reported that reduction in amniotic fluid was not detrimental to the fetus and on discontinuation amniotic fluid returned to normal.<sup>20,21</sup> But in our study one patient who continued taking Indomethacin, at home, without any follow up and surveillance returned with

severe oligohydramnios. Patient underwent emergency LSCS due to fetal distress and there was neonatal death at < 7days due to prematurity and sepsis.

The mean gestational age at delivery in our study was 36.28±1.41 weeks similar to study by Abhyankar et al.<sup>16</sup> In our study 17 (94%) had a good perinatal outcome similar to study conducted by Shrestha A et al and Abhyankar et al.<sup>11,16</sup>

Prostaglandins are important to maintain the patency of the ductus arteriosus during fetal life. Indomethacin therefore has a potential to cause ductal constriction. Therefore it is essential to follow the patient with regular ultrasound and fetal 2DECHO. Vermillon ST et al reported a dramatic reversal of ductal constriction after stopping Indomethacin and no significant adverse fetal outcome was attributed to Indomethacin therapy.<sup>22</sup> In our study there was no such complication observed.

#### Conclusion:

Indomethacin when used to treat symptomatic patients with Idiopathic Polyhydramnios significantly reduced amniotic fluid volume and prolonged pregnancy. But due to the effects on ductus arteriosus and other complications like oligohydramnios, patients should be regularly monitored with ultrasound and fetal 2DECHO. However further large scale controlled trials are required to understand the mechanism and to determine the safety of Indomethacin use.

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