Original Research Article

Intrahepatic cholestasis of pregnancy: An evaluation case-control study of perinatal outcome

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Received: 18-10-2020 / Revised: 30-12-2020 / Accepted: 21-01-2021

Abstract

Objectives: Intrahepatic cholestasis of pregnancy has been identified with a high recurrence of strange intrapartum fetal pulse, amniotic liquid meconium, rashness, and perinatal mortality. To decide if these unfavorable perinatal results could be improved with dynamic intercession, we assessed our outcomes. **Study Design:** We report an evaluation case-control investigation of 320 sequential patients 9 with intrahepatic cholestasis of pregnancy the executives with antepartum testing and dynamic mediation over a 2-year time span. **Results:** Our outcomes demonstrate a higher incidence of meconium staining in amniotic liquid at conveyance (25% V9 16%, $p < 0.05$) and spontaneou9 preterm conveyance (12.1% versus 3.9%, $p < 0.05$), without an expansion in the recurrence of the anomalous intrapartum fetal pulse (12% versus 11%, not critical), 5-minute Apgar score< 7 (2.0 versus 1.09), not huge), or perinatal mortality (18/1000 versus 13/1000, not critical). End: Antenatal testing and planned intercession of patients with intrahepatic cholestasis of pregnancy are related to a decrease of the recently revealed unfriendly perinatal results.

Keywords: Intrahepatic cholestasis of pregnancy, obstetric cholestasis, preterm labor, perinatal outcome.

Introduction

Intrahepatic cholestasis of pregnancy, or obstetric cholestasis, is a liver infection portrayed by broad sized skin pruritus that shows up during the second 50% of pregnancy, goes on until the finish of incubation, and vanishes a couple of days after conveyance." " It has a high pervasiveness in Chile' and Scandinavia' however is infrequently announced in different nations."'[1]

The infection has been identified with high perinatal complications, including a high perinatal death rate (110/1000), a high frequency of meconium staining of amniotic liquid (279a), anomalous intrapartum fetal pulse (FHR) (characterized as the presence of fetal bradycardia, tachycardia, or decelerations) (14%), and preterm conveyance (36%).' Others have revealed a perinatal mortality rate up to 200 for each 1000.' Fisk and Storey* supportive of represented that the result in such pregnancies could be improved with mediation when there is meconium staining in the amniotic liquid and fetal lung development is accomplished.[2] This methodology brought about a perinatal humanity pace of 35 for every 1000, on an actuated rashness pace of 19%, an unconstrained rashness pace of 44' o, and a cesarean area pace of 37%. For a very long time in our foundation patients with cholestasis of pregnancy have been conveyed by enlistment with oxytocin at 38 weeks' incubation or, if acceptance is contraindicated, by cesarean segment. [3] In the event that the patient has clinical jaundice, the inscription is performed at 36 weeks' growth if lung development is accomplished, or as before long as lung development is achieved."' To recognize whether the unfriendly result recently detailed in patients with cholestasis of pregnancy could be diminished, we assessed the perinatal result of 320 successive influenced patients in a 2-year time frame in our establishment, contrasted and a benchmark group. [4]

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Material and Methods

The clinical records of the relative multitude of patients who had cholestasis of pregnancy and who were conveyed between March 1, 2019, and April 30, 2020, at the Department of Obstetrics and Gynecology, Institute for Medical Sciences and Research Centre were taken. The standard group was shaped by picking the following patient who was conveyed after an instance of cholestasis of pregnancy, excluding the case just if the patient had cholestasis of pregnancy or the span of pregnancy was < 20 weeks. [5] The indicative rules for cholestasis of pregnancy were (1) ceaseless and summed up skin pruritus, dominatingly situated on all fours, which vanished in the puerperium, (2) nonattendance of obstructive gallstone illness analyzed clinically or by ultrasonography, (3) nonappearance of clinical proof of viral hepatitis, (4) nonattendance of fever or general disquietude, and (5) nonappearance of other skin or clinical problems that could deliver pruritus. \Vhen there was the uncertainty of the analysis or when jaundice or dull pee was distinguished, liver capacity tests were performed. In the event of clinical doubt of viral hepatitis, serum markers were tested. [6] The management of the patients with cholestasis of pregnancy included week by week pre-birth visits from the hour of analysis. At the point when an unexpected problem of pregnancy emerged (toxemia, untimely preterm crack of films, untimely work, little for gestational age), it was overseen as per standard obstetric consideration. [7] On account of preterm work, tocolysis was performed except if the gestational age was z 36 weeks. Control patients had customary pre-birth visits and a nonstress test (NST) when shown by obstetric conditions. At the point when the confusion of pregnancy emerged, it was overseen as per standard obstetric consideration.[8] Fetal reconnaissance of cholestasis of pregnancy included an everyday

maternal record of fetal developments and a weekly NST beginning at 34 weeks of pregnancy until conveyance. when the NST was nonreactive, a compression stress test (CST) was performed. In all patients at the hour of induction of pregnancy or the unconstrained beginning of work, amnioscopy was performed at whatever point conceivable and the presence of meconium in the amniotic liquid was noted.[9] Pregnancies with cholestasis of pregnancy were between 38 weeks of incubation by oxytocin enlistment of work when there was no obstetric contraindication; in any case, a cesarean segment was performed.[10] Patients with cholestasis of pregnancy and jaundice (all-out serum bilirubin b 1.8 mg/dl) with affirmed aspiratory maturity went through pregnancy interference following 36 weeks of incubation. Patients in the benchmark group anticipated the beginning of unconstrained work except if an inconvenience of pregnancy happened.[11] the prominent the event of medical confusions of pregnancy including (I) urinary lot disease (characterized as pee culture of u 10' state shaping units per milliliter), (2) toxemia (characterized by the Committee on Terminology of The American College of Obstetricians and Gynecologists)," (3) pre-term untimely burst of films (characterized as unconstrained crack of the chorioamniotic layers before the beginning of work in pregnancies 4 37 weeks of incubation), and (4) preterm work (characterized as the pres-ence of diligent uterine withdrawals, at any rate eight of every 60 minutes, and reformist cervical dilatation or progres-sive destruction, or a dilatation > 2 cm or destruction > 80%).[12] We likewise noted gestational age at conveyance and course of conveyance, a depiction of the FHR during work (abnor-mal FHR was characterized as the presence of any of the accompanying examples: bradycardia [FHR < 90 beats/min], serious variable decelerations, or late decelerations), amniotic liquid meconium at the interference of preg-nancy and conveyance, Apgar scores at 1 and 5 minutes, and intrauterine development hindrance (characterized as new-conceived weight < tenth percentile for gestational age ac-cording to the ordinary tables for our population).'" Measurable examination was performed with Student t test and jt" test when fitting. A Q esteem 0.05 was viewed as huge. [13]

Results

During the 2-year Period, 4916 conveyances were performed at our foundation. Of these patients, 320 (6.5%) were determined to have cholestasis of pregnancy. Of these, 34 (10.6%) had a clinical introduction of jaundice. There were no critical contrasts between patients with cholestasis of pregnancy and control patients in maternal age or equality (Table 1). In the entire time frame, 54 twin pregnancies happened, and 12 (22%) of them had cholestasis of pregnancy. In the benchmark group, two (3.7%) twin pregnancies were chosen ($p < 0.001$). 34 percent of multiparous ladies with cholestasis of pregnancy and 5.5% of controls had cholestasis of pregnancy in a past pregnancy, The chances proportion of repeat of the sickness in an ensuing pregnancy is 8.8 (95% certainty limit 4.2 and 19.2, $P<0.001$) (Table 1). Liver function tests were acted in 126 patients, where the determination of cholestasis of pregnancy was in question, to preclude other liver sicknesses. The most successive irregularities experienced in patients with cholestasis of pregnancy was a moderate expansion in soluble phosphatases (87%), aminotransferases (66%), furthermore, serum bilirubin (36%) (Table 11). - These outcomes are predictable with a cholestatic disorder with insignificant liver irritation or rot, in two patients in which viral hepatitis was suspected on a clinical premise, the serum markers were negative and the later clinical course of the sickness was steady with the determination of intrahepatic cholestasis of pregnancy. Table no 1 shows the complexities of pregnancy. There were no contrasts between patients with cholestasis of pregnancy and controls in the recurrence of urinary parcel.

Table 1: General characteristics of subjects and controls

	Cholestasis of pregnancy (n = 320)	Control (n = 320)
Maternal age (yr)*	27.5±5.5	27.6±5.1
Primiparous (%)	44	43
Previous cholestasis of pregnancy (%)	34.1	5.5
Multiparous (%)	56	57
jaundice(%)	10.6	0

*Mean *SD.
+P<0.01, odds ratio 8.8, 957c confidence limits 4.2 and19.2.

Table 2: Liver function test results in 126 patients with cholestasis of pregnancy

	Value*	**Abnormal results (%)**	**Normal ranges**
Total serum bilirubin (mg/dl)	**1.09 ± 1.01 (0.2-5.2)**	**36.1**	**0-1**
Alkaline phosphatase (U/L)	**243.1 ± 122 (4-587)**	**86.6**	**30-117**
Aspanate aminotransferase (U/L)	**106.1 ± 112.9 (6-565)**	**66.7**	**0-37**
Alanine aminotransferase (U/L)	**148.9 ±155.7 (3-736)**	**65.4**	**0-40**

*Mean ± SD and range.
Normal values were established in the group of normal pregnant women during the third trimester of pregnancy at Pontificia Universidad Clinical Laboratory.

Table 3: Complications of pregnancy in patients with cholestasis of pregnancy and controls

Complication	Cholestasis of pregnancy (n = 320)(%)	Controls (n = 320)(%)
Urinary tract infection	8.1	5.6
Preeclampsia	6.3	4.7

Preterm premature rupture of membranes	1.6	0.6
Preterm labor (excluding twins)	15.7	6.8*
Preterm delivery (< 37 wk) (excluding twins)		
Total	19.3	6.8
Spontaneous	12.1	3.9*
Cesarean section rate	25.9	16.9*

**P<0.05*

Contamination, toxemia, or preterm untimely burst of layers. Nonetheless, a 2.3-overlay increment in the recurrence of untimely work (barring twins) was noticed (15.7% vs. 6.8%, *P*< 0.05). A 2.8-overlap in-wrinkle in the occurrence of unexpected labor (< 37 weeks) was noticed (19.3% vs 6.8%, *P*< 0.05). More-finished, in the event that we consider just those with the unconstrained beginning of work, a triple expansion in unconstrained preterm conveyance was additionally noticed (12.1% versus 3.9%, p < 0.05). There was likewise a huge expansion in the frequency of cesarean area (25.9% vs I 6.9%, *P*< 0.05). The ob-served expanded cesarean segment rate was primarily due to a higher (however not huge) rate of the elective cesarean segment (16.3% vs 9.6%). The intrapartum cesarean segment rate was comparable between the two gatherings (9.7% and 6.4%, not huge) and 48% of those in the cholestasis of pregnancy bunch were because of the disappointment of work to progress. In 229 of the 320 patients with cholestasis of pregnancy, an NST was performed inside the multi-week before conveyance. Of these, 223 (97.4%) were responsive and six were nonreactive. In ensuing CSTs of five cases, four were negative. The one instance of a positive CST was acquired at 31 weeks in a lady with serious toxemia. The infant was conveyed by cesarean segment and weighed 985 gm (< 10th percentile), with Apgar scores of 9 at 1 and 5 minutes. The one situation where a CST was not performed was a patient at 32 weeks' development with the untimely crack of films and meconium staining of amniotic liquid. She had a past cesarean area, and the choice was made to again play out a cesarean segment. A solid infant of 1720 gm was conveyed, with Apgar scores of 9 at birth and 5 minutes. The leftover 91 NSTs not indicated represented patients conveyed before 34 weeks' gestation (11%), elective cesarean segment performed 8 days

Table 4: Perinatal outcome in patients with cholestasis of pregnancy and in controls

	Cholestasts of pregnancy (%)(n = 320)	Control(%)(n = 320)
Meconium staining		
At admission for delivery*	13.4	6.8+
At delivery	24.8	15.5+
Abnormal FfIR pattern	12.8	11.3
Apgar score<7 at 1 min	7.8	7.2
Apgar score <7 at 5 min	2.2	1.3
Small for gestational age	6.3	4.4

*n = 234 in cholestasis of pregnancy group and n= 250 in the control group.+P<0.05

Table 5: Perinatal mortality (per 1000 live births) in cholestasis of pregnancy and controls

	Cholestasts of pregnanty (n = 328)		Control (n = 319)	
	No.	Mortality per 1000live births	No.	Mortality per 1000 live births
Stillbirths	4	12	3	9
Neonatal deaths	2	6	1	3
Perinatal mortality	6	18	4	12
Correctedperinatal mortality*	6	18	2	6

*Excluding malformations.

after the past pre-birth visit (64%), and NSTs not performed in light of the fact that the patient neglected to go to the pre-birth ap go-to people t and went to the medical clinic in labor (25%). The perinatal result appears in Table IV. In the cholestasis of pregnancy bunch, there was a higher frequency of meconium staining in amniotic liquid at the hour of the choice to convey (*P*< 0.05) or at conveyance (p < 0.05). There were no huge contrasts in the occurrence of unusual intrapartum FHR designs, Ap-gar scores at 1 and 5 minutes, or the recurrence of little for-gestational-age infants.

Perinatal mortality appears in Table V. No significant contrasts were seen in the fetal, neonatal, and complete or remedied (for distortions) perinatal death rates between the gatherings. The four stillbirths in the cholestasis of pregnancy bunch were somewhere in the range of 33 and 38 weeks of development. None of the moms had complexities of pregnancy, all the hatchlings were appropriate for gestational age, and the NST performed inside multi 1 week of conveyance (at 2, 5, and 6 days before the assessed stillbirth day) was responsive in three of the four embryos. The other baby didn't have an NST on the grounds that demise happened before 34 weeks of growth. In three cases there was meconium staining of amniotic liquid, and in the other case, the amniotic liquid was hemorrhagic.

The three stillbirths in the benchmark group introduced the inconveniences of pregnancy. Case number one was enormous for gestational age, the subsequent case had a deadly central nervous framework abnormality (prosencephalon, Kundrat's sort I)," and the third case was related with maternal pyelonephritis and a huge for-gestational-age hatchling. With respect to neonatal mortality, in the examination bunch, the primary neonatal demise was an infant who kicked the bucket 23 hours after conveyance optional to a gathering D Stre§/otmcus sepsis. In the second case, an abruptio placenta was analyzed and a crisis cesarean segment was performed. The newborn child was brought into the world with serious asphyxia and kicked

the bucket 8 days after the fact from multisystem disappointment. In the benchmark group, the solitary demise was an infant with lung hypoplasia because of obstructive nephropathy.

Discussion

The reason for cholestasis of pregnancy is still ineffectively sawed, however, its antagonistic effect on perinatal out-come has been well documented. [14] The aftereffects of the current examination show that with dynamic intercession of such pregnancies the perinatal result improves in correlation with past reports and results in paces of a fruitful result like those saw in the benchmark group.

Cholestasis of pregnancy was recently identified with amniotic liquid meconium, preterm conveyance, high perinatal mortality, and anomalous intrapartum FHR. [15] Our information upholds a twofold expansion in the frequency of antepartum amniotic liquid meconium and a triple expansion in the occurrence of unconstrained unexpected labor (controlled for n 'in pregnancies) contrasted and the controlled populace.[16] Our huge arrangement doesn't uphold the high rate of stillbirth and unusual intrapartum FHR in cholestasis of pregnancy revealed by others, which has led to a high rate of induced unexpected labor and cesarean segment." However, the corrosive (fetal malformations) perinatal m[...] with jaundice, where we conveyed at 36 weeks' gestationif pulmonary maturity was recently shown.[17] At present we do not know the pathogenesis of the expanded amn[...] fetal sheep the imbuement of cholic corrosive (1.6 mmol/min from 120 days' incubation, term 147 x 5 days) brought about a higher frequency of amniotic liquid meconium, untimely work, and unexpected labor contrasted and the benchmark group." These investigations propose a part for the bile acids in the expanded occurrence of amniotic liquid meconium and preterm conveyance.[18] Be that as it may, these investigations and our own didn't uphold a connection between unusual intrapartum FHR and amniotic liquid meconium. Because bile salts stimulate colonic motility in Vivo and in vitro,[19] "I "it can be postulated that the appearance of meconium in cholestasis of pregnancy is most likely brought about by such stimulatory impact. Despite the fact that this information appears to be alluring, the specific relationship between these perceptions and the high recurrence of untimely work isn't completely perceived.[20] Bile corrosive can invigorate prostaglandin discharge both in vivo and in vitro," and it is conceivable that prostaglandins delivered from uterus or decidua can trigger the biomolecular occasions identified with parturition.

The reasoning for the utilization of NST in the antepartum administration of cholestasis of pregnancy is controversial.[21] The rate of unusual NSTs was equivalent to that in an unselected populace,' and in the five cases with nonreactive NSTs in which a CST was performed just one instance of fetal trouble was analyzed and the patients had another sickness cycle that could clarify without help from anyone else the positive CST. What's more, in three of the four stillbirths in our investigation the NSTs were receptive inside 2, 5, and 6 da7• before fetal demise, and in the other case, the NST was not acted as per our convention.[22] Additionally, in every one of them, the maternal record of fetal action was ordinary until a couple of hours before admission to the medical clinic.[23] A new report utilizing the fetal biophysical profile was not definitive, mostly due to the nonappearance of fetal mortality and dreariness of that arrangement."' More information is needed to affirm the utility of week after week or twice-week after week NST or biophysical profiles in the antepartum administration of these preg-nancies. [24]

The reasons for stillbirth in the cholestasis of pregnancy are obscure. It has been accounted for that placentas got from ladies with cholestasis of pregnancy have a reduction in the size of the intervillous space, because of the growth of the trophoblast and edema of the villous stroma."[25] It was recommended that these progressions could weaken fetal oxygenation by lessening the maternal bloodstream to the intervillous space.[26] In a couple of patients with cholestasis of pregnancy, estimations of intervillous bloodstream by the xenon 133 technique exhibited clashing outcomes on the grounds that no progressions or diminishes in the bloodstream to the intervillous space were noted. '

Likewise, umbilical corridor Doppler estimations (Pourcelot list) in 15 patients with intrahepatic cholestasis of pregnancy exhibit no critical changes contrasted and a controlled populace.[27] We analyzed cholestasis of pregnancy essentially on a clinical premise. Different specialists included just those patients with the clinical image of the illness and with expanded fasting plasma bile acids.[28] Estimation of bile acids in pregnant ladies exhibits that 20Ko of ladies with ordinary cholylglycine levels and 489c of those with raised cholylglycine levels have pruritus." However, when sequential estimations of bile acids or liver capacity tests are acted in patients with cholestasis of pregnancy, an incredible fluctuation is observed in a similar patient all through the development of the sickness, plasma esteems going from ordinary to abnormal in an irregular manner." " Because up to 45Yo of patients with a clinical conclusion of cholestasis of preg-nancy might not have anomalies in a solitary example of fasting plasma bile acids and about 507c of them show an ascent after a test feast (affirming the flawed hepatic bile corrosive transport),"' we feel that the clinical picture is sufficient to build up the determination of cholestasis of pregnancy.[29] Likewise, no reasonable connection between maternal bile [...] outline, this investigation shows that pregnancies confounded by clinically analyzed cholestasis of pregnancy present a high danger for preterm work and meconium staining of amniotic liquid.[30] Nonetheless, with dynamic mediation in such pregnancies, the perinatal result was equivalent to that of controls and better than that recently detailed.

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Conflict of Interest: Nil
Source of support:Nil