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Role of Bacterial Infection in Preterm Birth and Study of Expression of TGF-BETA in Preterm Birth.

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ABSTRACT:

Background: World health still struggles with Preterm Birth (PTB), which causes infant death and morbidity. 5% to 25% of pregnancies worldwide result in preterm birth, defined as delivery before 37 weeks. This study will examine if bacterial infections cause premature labour and compare TGF-BETA gene expression in preterm and full-term newborns.

Methods: The research took performed at BHU in Varanasi, Uttar Pradesh, from September 2019 to May 2021. Pre-eclampsia and multiple pregnancies were excluded, however preterm labour before 37 weeks was included. SPSS 21.0 was used to compare socio-demographic criteria, placental parameters, and genetic expression.

Results: The study included 100 pregnant women, 50 of whom had preterm births and 50 full-term births. In particular, 56% of preterm births occurred in women aged 20-24 (p=0.016), demonstrating significant age variance. Both abortion history (p=0.517) and delivery method (p=0.423) did not significantly differ across groups. Compared to controls (10%), preterm patients had 75% higher placental tissue bacterial growth (p-value 0.001). TGF-BETA expression was similar in full-term and preterm deliveries (p=0.412).

Conclusion: PTB is the greatest cause of neonatal mortality and morbidity and has a complex cause. The study's findings that bacterial illness is strongly linked to preterm birth emphasise the need for better infection control in pregnant women. Despite the strong bacterial association, preterm and full-term births had similar TGF-BETA expression, suggesting that other inherited or environmental factors may contribute to PTB.

Introduction

Worldwide, infant mortality and morbidity are most commonly caused by PTB. Preterm birth is defined by the World Health Organisation (WHO) as the delivery of a baby before the 37th week of gestation or within 259 days from the first day of a woman's last menstrual period (LMP) [1]. Preterm labour is estimated to affect anywhere from 5% of the global population in industrialised nations to 25% in developing nations, yet reliable data on this topic is lacking for the past few years. In industrialised nations, the prevalence has remained around 5% to 10% for many years. Preterm delivery accounts for 28% of all neonatal deaths (death within 7 days) [2].

Objective

- Determine the impact of bacterial infection on premature labour.
- Researching the levels of the TGF beta gene in the chorionic villi of both full-term and preterm babies.
- To learn more about what causes premature birth.

Incidence

Developing nations, such as India, bear a disproportionate share of the cost of preterm labour.

Worldwide, there is a lack of up-to-date accurate data on the occurrence of preterm labour; however, estimates vary from 5% in industrialised nations to 25% in developing nations. In industrialised nations, the prevalence has remained around 5% to 10% for many years. A study conducted by [3] concluded Each year, 3,341,000 babies are born prematurely in India, and 361,600 children under the age of five lose their lives as a direct result of preterm problems. 2014 (UNICEF, WHO, World Bank)

Etiopathogenesis

Preterm birth is associated with a complicated and poorly understood pathophysiology that involves multiple factors. The uterine activation, labour, and delivery processes are influenced by a variety of environmental, physiological, and genetic factors that are linked to premature birth. Preterm birth is difficult to predict due to its complex aetiology [4].

Role of infection

Preterm labour and delivery have been linked to infections that develop during pregnancy. Pathophysiology of preterm labour and delivery includes infection. Based on where the microorganisms are located, there are two main types of intrauterine infections: intra-amniotic and extra-amniotic infections [5]. Since the amniotic cavity is usually sterile, the discovery of any microorganism in the amniotic fluid indicates that microbes have invaded the body.

Bacterial vaginosis

The vaginal environment normally contains many different kinds of bacteria, but under normal physiological settings, the vast majority about 95% are H2O2-producing lactobacilli. These bacteria prevent the growth of other microbes by keeping the vaginal pH acidic [6]. The anaerobe to aerobe ratio changes to 100:1 to 1000:1 when BV is present, the vaginal pH rises, and the amount and quality of H2 O2-producing lactobacilli fall [7]. The amount rather than quality of the microbes present determines whether an environment is considered healthy or unhealthy for vaginal bacteria.

Urinary tract infections

Pregnant women are just as susceptible to the same microorganisms that cause UTIs as everyone else. Although 80% to 90% of illnesses are caused by Escherichia coli, other non-gram bacilli such Klebsiella pneumoniae and proteus mirabilis also play a significant role [8]. Urease activity and the production of urinary calculi by Proteus, klebsiella, and numerous Enterobacteriaceae species make these bacteria potential infection vectors. The second most frequently isolated uropathogen is staphylococcus saprophyticus, a coagulase-negative cocci [9]. The hematogenous pathway can transmit less frequent uropathogens such as Staphylococcus aureus and Mycobacterium tuberculosis [10].

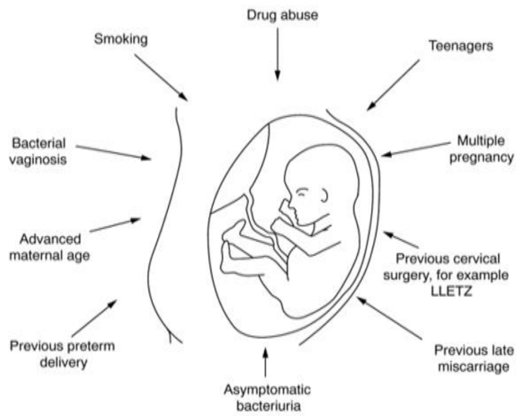

Figure 1 Risk factors for preterm labor

Methodology

Study design

Observational, prospective and case control study.

Study period

September 2019 – May 2021

Study place and sample size

Researchers from Banaras Hindu University in Varanasi, Uttar Pradesh, and the Institute of Medical Sciences at BHU's Department of Obstetrics and Gynaecology worked together on this study. The patients who participated in the study were those who visited the hospital's outpatient department or were casualties. 20 cases and 10 controls are used for bacterial infection identification, whereas 50 cases and 50 controls are used for TGF-β expression.

Inclusion criteria

Patients who experience preterm labour have a gestational age below 37 weeks. Women who were given

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the gestational age were able to give birth after 37 weeks of pregnancy.

Exclusion criteria

a) Pre-eclampsia

b) Chorioamnionitis

c) Twin or multiple pregnancies

d) Hydramnios

e) Uterine anomalies

f) Fetal anomalies

g) Intra uterine fetal death

h) Positive history of maternal diabetes

Ethical approval

The Institute Ethical Committee at Banaras Hindu University's Institute of Medical Sciences provided the necessary ethical clearance.

Statistical Analysis

Standard proforma was used to capture the data of the socio-demographic factors, placental parameters, and genetic study. The data was examined using SPSS version 21.0 software, which generated the necessary tables and graphs. The numbers and percentages for different case and control features were calculated.

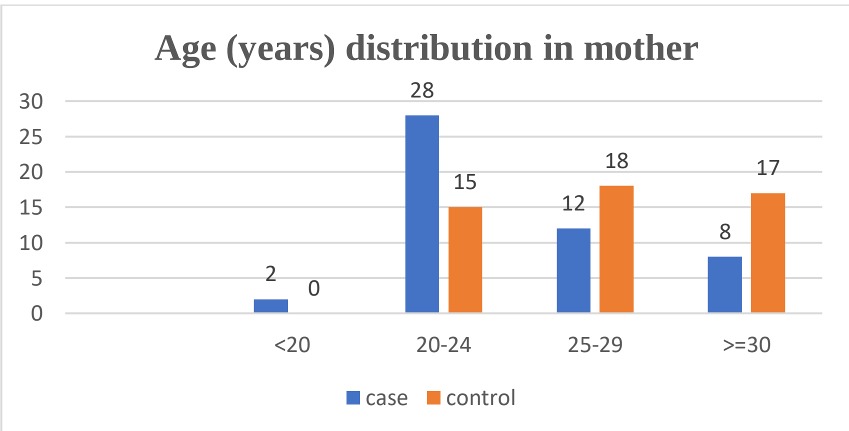
Result

The study included 50 cases who delivered before 37 weeks of gestation and 50 controls who delivered at term.

Table 1 Age distribution of mother

Age in years	Case		Control		Total		
	Count	N %	Count	Column N %	Count	Column N %	p-value
<20	2	4.0%	0	0.0%	2	2.0%	.016
20-24	28	56.0%	15	30.0%	43	43.0%	
25-29	12	24.0%	18	36.0%	30	30.0%	
>=30	8	16.0%	17	34.0%	25	25.0%	
Total	50	100.0%	50	100.0%	100	100.0%	

Age distribution of the 100 study participants by case and control groups is shown in the table. The p-value of 0.016 suggests a significant age difference between the two groups. The case group is 56% 20–24, while the control group is more evenly distributed with 36% 25–29. Compared to 34% of controls and 16% of cases, just 4% of case group participants are 20 or older.



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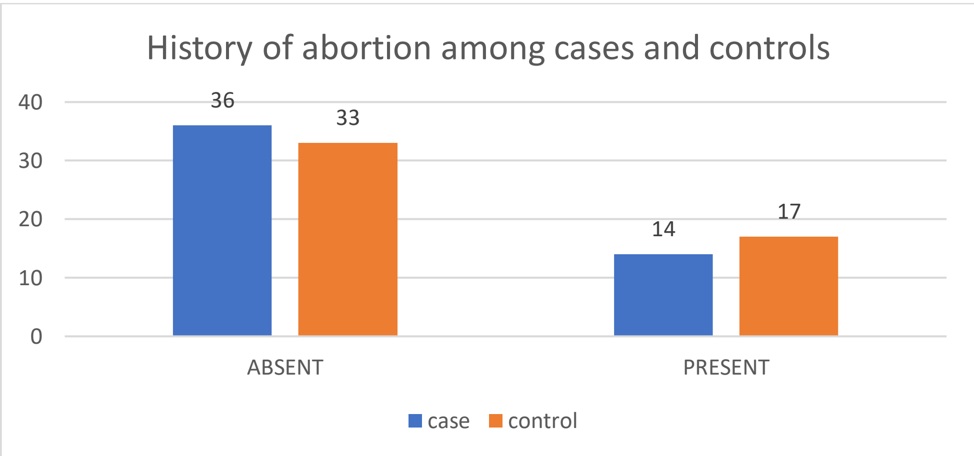
History of Abortion

Table 2 History of Abortion

H/O Abortion	Case		Control		Total		p-value
	Count	Column N %	Count	Column N %	Count	Column N %	
ABSENT	36	72.0%	33	66.0%	69	69.0%	0.517
PRESENT	14	28.0%	17	34.0%	31	31.0%	
Total	50	100.0%	50	100.0%	100	100.0%	

Data compares case and control groups' abortion histories. Of the cases, 28% had an abortion history, whereas 72% did not. 34% of control group women had abortions, whereas 66% had none. Abortion history did not differ between case and control groups (p = 0.517). This suggests that abortion histories were similar in both groups, which may not affect the condition or outcome under inquiry.



Mode of delivery

Table 3 Mode of delivery

MOD	Case		Control		Total		p-value
	Count	Column N %	Count	Column N %	Count	Column N %	
LSCS	24	48.0%	28	56.0%	52	52.0%	0.423
SVD	26	52.0%	22	44.0%	48	48.0%	
Total	50	100.0%	50	100.0%	100	100.0%	

Case (n=50) and control (n=50) groups are compared by delivery method in the table. The p-value of 0.423 showed no significant difference in delivery modes between groups. LSCS was conducted by 48% of cases

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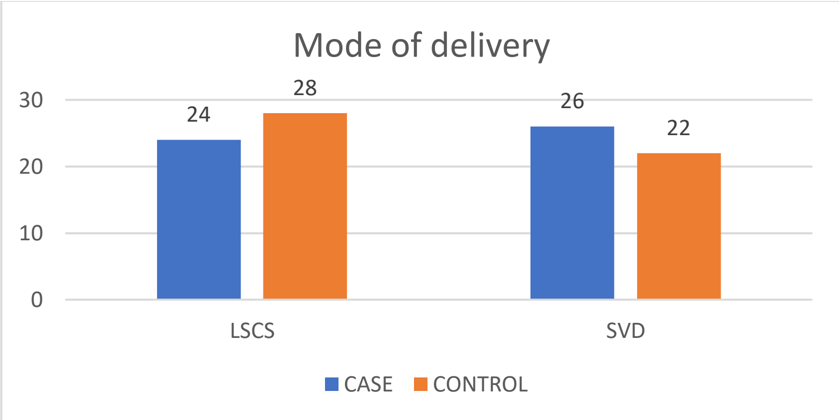
JCHR (2024) 14(3), 3511-3519 | ISSN:2251-6727

and 56% of controls, while SVD was performed by 52% and 44%. This study shows no statistically significant association between delivery mode and case or control status, as revealed by the balanced distribution of delivery modes in both groups and the overall count and column percentages.

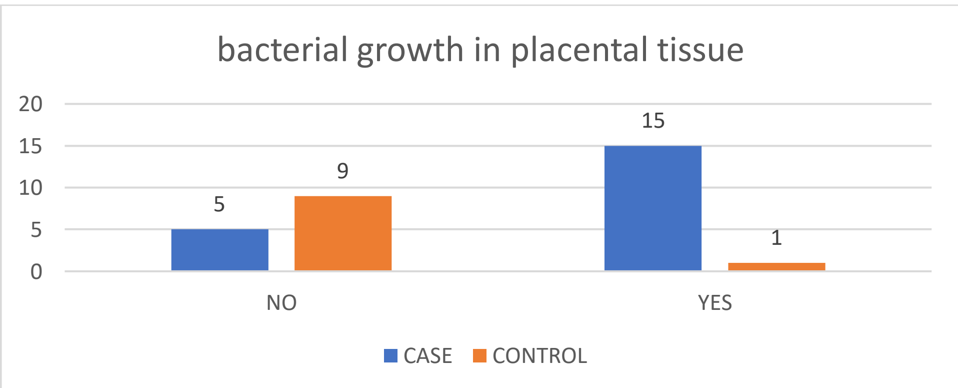


Bacterial growth seen in placental tissue

Table 4 Bacterial growth seen in placental tissue

BACTERIAL GROWTH ON PLACENTAL TISSUE	Case		Control		Total		p-value
	Count	Column N %	Count	Column N %	Count	Column N %	
NO	5	25.0%	9	90.0%	14	46.7%	.001
YES	15	75.0%	1	10.0%	16	53.3%	
Total	20	100.0%	10	100.0%	30	100.0%	

The results show significant differences in placental tissue bacterial growth between case and control groups. 75% of cases (15/20) had bacterial growth, compared to 10% of controls (1/10). Bacteria were absent in 25% of cases and 90% of controls. Bacterial growth on placental tissue was significantly linked with case group membership ($p = 0.001$). This shows that the case group's defining trait may be higher bacterial colonisation.



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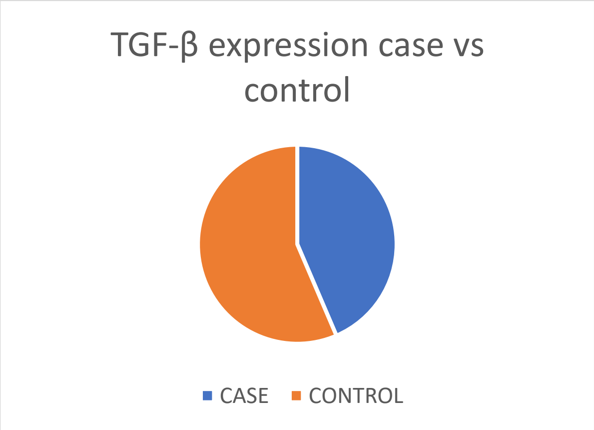
TGF-BETA EXPRESSION

Table 5 TGF-BETA EXPRESSION

	TGF-Beta	p-value
CASE	**2.33686612**	0.412
CONTROL	**3.02942333**	

The control group had 3.03 TGF-Beta, while the case group had 2.34. The two groups may have had different TGF-Beta levels, but the p-value of 0.412 shows an insignificant difference.



Discussion

PTB, a major source of perinatal disease, mortality, and long-term disability, remains a major issue in obstetrics. The World Health Organisation (1977) defines preterm birth as any delivery before 37 weeks or 259 days after a woman's last menstrual cycle. Every year, 15 million babies are born prematurely and 1 million die. PTB is the largest cause of prenatal mortality, illness, and impairment in children under five in the developed world [11]. [12] found that preterm neonates had a greater risk of serious perinatal issues. Most premature newborns live healthy, productive lives, but a significant percentage develop chronic illnesses and disabilities. Perinatal care costs and lifelong disability affect individuals, families, and society [13]. The study included 100 pregnant women with singleton pregnancies who were over 28 weeks gestational age, 50 of whom were cases (those with ACOG-defined preterm labour symptoms who gave birth before 37 weeks) and 50 of whom were controls. The study divided moms by age into four groups: under 20, 20–24, 25–29, and beyond 30. Patients aged 20–24 account for 56% of cases. About 70% of full-term mothers are above 25. This study is significant with a p-value of 0.016. The average maternal age has slowly increased in recent decades. Young mothers (≤ 19 years old) and older mothers (≥ 35 years old) have a higher risk of adverse maternal and infant outcomes, including preterm birth, poor foetal growth, low birth weight, and neonatal mortality.

Effect of smoking/tobacco chewing/alcohol on preterm labour

Everyone in this study was clean on smoking, drinking, and substance abuse. Most pregnant women in the US do not smoke, drink, or chew tobacco. Smoking increases the risk of premature birth [14]. Nicotine and carbon monoxide are strong vasoconstrictors that cause placental damage and limit uteroplacental blood flow, but the biological effects of most of the more than three thousand chemicals in cigarette smoke are unknown. Both babies are premature due to foetal growth limitation. Smoking may promote spontaneous premature delivery due to systemic inflammation [15].

Association between stressful conditions among mothers and preterm birth

Stressful conditions such obstetric cholestasis, anaemia, fibroid uterus, urinary tract infection, pregnant hypertension, and gestational diabetes mellitus were rare (10/50). Only six of fifty controls were stressed. The p-value is 0.604, indicating no statistical significance. We can conclude that premature labour is not linked to non-stressful conditions.
Researchers found a relationship between gestational hypertension, diabetes, shorter gestational age, and medically advised early labour [16]. Long hours and intensive physical labour under stress may promote preterm birth. Psychological or social stress may cause premature birth through corticotropin-releasing hormone. Stressed women had higher C-reactive protein levels in their blood [17].

Journal of Chemical Health Risks
www.jchr.org
JCHR (2024) 14(3), 3511-3519 | ISSN:2251-6727

History of preterm birth and its relation with preterm birth

Five of 50 case babies were preterm, compared to one of 50 controls. A history of preterm birth does not statistically predict preterm birth in the present pregnancy. [18] found that preterm birth risk increases with closeness to previous deliveries. Recurrence risk in women with a history of preterm deliveries ranges from 15% to 50% or more, depending on the number and gestational age of prior deliveries. Mercer and colleagues found that a woman's following pregnancy was 2.5 times as likely to be preterm. According to [19], the gestational age of a previous preterm birth inversely affects the chance of another premature birth. Repeated spontaneous preterm births may be caused by intrauterine infections. [20] found that diabetes, hypertension, and obesity typically persist between pregnancies, causing preterm births.

Association between PV bleeding and preterm labour

The control subjects had no history of prevaginal bleeding, but 2% of women who delivered birth before the due date did. A 0.315 p-value means the study is not statistically significant.
Placental abruption or praevia causes vaginal bleeding and a high risk of preterm delivery. However, subsequent preterm birth is related with first- and second-trimester bleeding not caused by either of these diseases [21]. PPROM and thrombin generation following vaginal bleeding may be linked because they can trigger uterine contractions and proteolytic activity.

Bacterial infection and its association with preterm birth

In 75% of cases, placental tissue had bacterial growth, compared to 10% of term births. Preterm delivery is associated with placental tissue bacterial infection (p=0.001). PCR and biochemical techniques have confirmed Enterococcus faecalis proliferation. This study included about three quarters of low- and middle-income participants. Poor cleanliness may promote digestive tract nosocomial infections. Due to innate immune system activation, intrauterine infections can trigger premature labour. Microbes release endocannabinoids and inflammatory cytokines, which cause the body to produce prostaglandins and matrix-degrading enzymes. PPROM occurs when the foetal membranes' extracellular matrix dissolves, while prostaglandins compress the uterus.

Expression of TGF-β1 and its association with preterm birth

Preterm patients had reduced TGF-β1 expression in placental tissue compared to controls, although the difference was not significant (p value= 0.4120). TGF-β1 levels in pregnant women's plasma were significantly greater than nonpregnant controls and adults (2-18 ng/mL).
Reducing TGF-β1 expression in preterm delivery patients aligns with studies on decidual tissue from patients with recurrent spontaneous abortion (RSA). TGF-β1 may play a role in the development and progression of RSA via regulating immunological tolerance. TGF-β regulates endometrial cell mortality and proliferation during embryo implantation, according to research.
Late-onset pre-eclampsia (PE) is associated with reduced TGF-β1 expression in both mother and baby's blood. In early-onset PE, no difference was seen and PE raises premature birth risk. TGF-β1 may play a role in later pregnancy, especially preterm birth, as it regulates trophoblast cell invasion and fetal-maternal immunological tolerance in early pregnancy.

Conclusion

Preterm birth causes severe prenatal morbidity and mortality. Labour timing is difficult to predict. This is likely because several variables can cause preterm labour, and different women have distinct symptoms that lead to premature delivery. This research aims to identify factors that enhance the risk of premature labour, assess the impact of bacterial infection, and investigate the link between TGF-β expression and preterm delivery. In this study, fifty pregnant women who were 28–37 weeks along and had premature labour signs were compared to fifty who gave birth at term. Each case was thoroughly evaluated utilising laboratory, clinical, and patient history. Critical analysis and comparison to other studies were done. We examined the relationship between TGF-β expression and preterm labour in 50 cases by detecting it in placental tissue. We studied bacterial infection function with 20 cases and 10 controls. The 20–24 age group has the highest preterm birth rate (56%). Most premature babies are born between 34 and 37 weeks. First-time mothers have 54% preterm deliveries. Patients without a delivery date have a 60% premature birth rate. Preterm births are more likely in poorer families. Abortion history does not predict preterm birth. Premature births increased membrane rupture risk (34%). There is no evidence that smoking, alcohol, or substance abuse cause premature labour. PV haemorrhage does not cause premature birth. The majority of preterm babies (52%), were born spontaneously via vaginal delivery. Preterm birth rates are unaffected by baby gender. This study shows a mere 52% male predominance. Most preterm babies (72%) weigh 2–2.5 kilogrammes. The 50% neonatal intensive care unit admission rate for preterm babies is substantially higher than for full-term neonates. Preterm delivery increases bacterial infections by 75%. There is no substantial difference in TGF-β expression between patients and controls.

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