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Original Article

Risk Factors Leading to Preterm Deliveries Among the mothers in Jaffna District, Sri Lanka

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Abstract

Health status of pregnant woman is associated with the risk of preterm delivery. An institutional-based descriptive study was conducted among 173 mothers who delivered preterm babies at the Teaching Hospital, Jaffna, Sri Lanka.

Median gestational age of the preterm babies was 35.0 (±1.9) weeks. The mean birth weight of the preterm babies was 2.2 (±0.6) kg, and 54.3% of preterm babies were males. Nearly half of the mothers (54.9%) did not have complications during pregnancy, while pre-rupture of membrane (25.4%) and hypertension (13.3%) were in higher prevalence among those who had the complications. The risk factors of very preterm deliveries observed were the mothers who were primies (OR: 3.021), the mothers who maintained interpregnancy interval of <1 year (OR:1.117), had sexual intercourse before two weeks of delivery (OR:1.607) and were diagnosed with pregnancy complications (OR:1.695).

The prevalence of very preterm birth is low. However, based on the risk factors linked to very preterm identified by this study, implementation of interventions focusing on improving the profile of the pregnant mothers may serve as a protective factor for reducing very preterm birth.

Keywords

Pregnancy health, very preterm, moderate to late preterm, Jaffna District

Introduction

Births occurring before the completion of 37 weeks of gestation are known as preterm birth (1). Preterm births are categorized as very preterm (28 to <32 weeks) and moderate to late preterm (32 to <37 weeks) (1). Despite the advances of neonatal and obstetric care practices in Sri Lanka, the preterm birth rate in Sri Lanka ranges between 10 and 15 per 1000 live births (2).

Pregnancy illnesses such as pregnancy-induced hypertension, gestational diabetes mellitus anemia (2), pre-pregnancy overweight, family history of diabetes, women with chronic hypertension, number of pregnancies, placental abruption, family history of preterm birth, pre-rupture of the membrane and multiple pregnancies (3) have been associated with adverse birth outcomes. Hence, this study was carried out to investigate the pregnancy risk factors which could be associated with preterm deliveries.

Method

An institutional-based descriptive study was conducted at Teaching Hospital, Jaffna (THJ) Sri Lanka between October 2015 and February 2017 among 173 mothers who delivered preterm babies at the gestation between 28^{+1} and 36^{+6} weeks. The mothers who were residing in Jaffna Regional Directorate of Health Service (RDHS), and delivered very and moderate to late preterm babies in THJ were recruited for this study. The mothers who could be selected under inclusion criteria, and gave their consent were considered as sample of this study.

The sample size calculated was 170 based on Daniel formula (4) and a national study of Kiridana et al. (5)

A pre-tested interviewer-administered questionnaire included pregnancy conditions such as antenatal care clinic visits, body mass index at first registration of clinic, parity, inter-pregnancy interval, contraceptives use prior to conception, subfertility treatment, previous history of preterm birth/ abortion/ ceasarean section, pregnancy complications, multiple pregnancies and sexual intercourse prior to two weeks delivery. The gestational age was calculated as it was on the delivery date based on the Last Regular Menstrual Period (LRMP). Data were analysed using Statistical Package of Social Sciences (SPSS), version 23.0. Pregnancy risk factors for very preterm and moderate to late preterm delivery were identified using bivariate analysis. P<0.005 was considered statistically significant.

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Ethical approval was obtained from the Ethics Review Committee, Faculty of Medicine, University of Jaffna, Sri Lanka (J/ ERC/ 14/ 58/ NDR/ 0113). Informed written consent was obtained from the mothers. Confidentiality and anonymity of all records were ensured.

Results

Teaching Hospital, Jaffna provides Perinatal Care Services including Special Neonatal Care. The mothers (n=173) were selected from three maternity wards of this hospital.

Birth profile

Mean gestational age of the preterm babies was 35.0 (±1.9) weeks which ranged between 28^{+1} and 36^{+6}. Mean birth weight of the preterm babies was 2.2(±0.6) kg which ranged between 0.8 and 4.2 kg, and 54.3% of preterm babies were males. The frequency of moderate to late preterm delivery was 91.9% (n=159). The ratio between the very preterm to moderate to late preterm was 1: 11.4 (14 nos.:159 nos.).

Maternal profile

The age of the mothers ranged between 17 to 45 years with the mean age of 28.8 (±6.4) years. Majority (84.4%) of the mothers were aged between 20 and 34 years, while 4.6 and 11.0% of them were teenagers and over-aged respectively. Among the mothers who delivered preterm babies, all were Tamils and, majority were Hindus (72.3%), married (98.8%), studied up to General Certificate of Education- Ordinary Level [GCE (O/L), 79.8%], housewives (86.1%), receiving monthly income per person > 4,340 LKR (62.4%), and living in extended families (75.7%).

Majority of the mothers (96.0%) had registered at the Public Health Midwives offices. The mean BMI of the mothers was 23.7 (±4.6) kgm^{-2}, and ranged between 13.8 and 36.0 kgm^{-2}. Primi mothers were 47.4%. Majority (60.4%) of the mothers who had the parity above one, maintained 1 to 3 years of interval between two subsequent pregnancies. Sixty percent of the mothers reported that they did not use contraceptives within 4 to 12 months before conception. The mothers who underwent In Vitro Fertilization subfertility treatment was 1.2%. Previous history of preterm deliveries, abortion, and cesarean section were recorded among 15.0, 17.3, and 9.8% of the mothers respectively.

Pregnancy complications such as pre-rupture of the membrane (25.4%), hypertension (13.3%), anemia (9.2%), and gestational diabetes (5.8%) were observed in higher numbers, while more than half of the mothers (54.9%) were not diagnosed with pregnancy complications. More than half of the mothers (52.8%) reported that they had sexual intercourse during the last two weeks before the delivery.

Discussion

The frequency of moderate to late preterm (91.9%) (Table 1), and ratio between the very preterm to moderate to late preterm (1: 11.4) was in agreement with the statistics of Teaching Hospital, Jaffna, where it was during 2016 and 2017 were 89.4, and 87.4% respectively and 1:8.4 and 1:6.9 respectively (6). (Table 1)

Table 1: Birth of preterm babies at different gestational periods.

Babies		
Gestational Period (Weeks)	**No.**	**Percentage**
28^{+1}-31^{+6}	14	8.1
32^{+0}-36^{+6}	159	91.9
Total	**173**	**100.0**

Pregnancy details

Attending the Antenatal Clinics

Registering with the Public Health Midwives offices as soon as of pregnancy is mandatory in Sri Lanka and mothers can gain adequate knowledge regarding the birth outcomes via sharing the experiences under close supervision (7). Under such situation, about 4% of the mothers recruited for this study have not registered with the Public Health Midwives offices, while the statistics of Sri Lanka also reported that it was 2.2% (8). Among those who had not attended the antenatal clinic (n=7), 42.8% (n=3) had the pregnancy complications such as gestational diabetes (n=2) and hypertension (n=1). However, there are insufficient evidence to conclude that attending the antenatal clinic would reduce the preterm birth among socially disadvantaged or vulnerable populations when compared with standard models of antenatal care (9).

BMI of the Mothers

The mean BMI of the mothers was of overweight category. In this study, 17.3% of the mothers had the BMI of less than 18.5 kgm^{-2}, while 39.9% of mothers had the BMI above 25.0 kgm^{-2}.Thus the number of mothers who were obese was two times higher than those were underweight.Sri Lankan statistics stated that there is a decline in underweight maternal population of as 20.2, 18.8 and 17.5% during 2015, 2016,

and 2017 respectively (13). In the present study, the mothers with overweight/obesity and underweight have delivered very preterm in the frequency of 5.8 and 1.2% respectively.

Parity of mothers

The frequency of primi mothers was 47.4%, and second, third, fourth, fifth, and seventh parity mothers were 28.9, 15.0, 3.5, 4.6, and 0.6% respectively. This frequency distribution indicated that, primi mothers had higher percentage of preterm deliveries. In addition to that, 12.2% of the primi mothers have delivered very preterm babies. Previous studies had also endorsed our observation (14-15).

Inter-Pregnancy Interval

Very preterm deliveries was 6.2% among the mothers who maintained less than one year of interpregnancy interval. Inter-pregnancy interval is considered as short if itis less than one year (16). In the present study, 60.4% maintained above one year interpregnancy interval, and it matched with a previous study where it was 90.1% (17).

Contraceptive Usage

Family planning determines the spacing of pregnancies, and it is achieved through information, education, and the use of contraceptive methods (1). In the present study, 39.8% used contraceptive method, and the very preterm deliveries was 5.8% among them. Oral contraceptive pills (42.0%) and Depo- Provera Injection (33.3%) were the major types of contraceptives. It matched with a study indicated that 59.4% of the Sri Lankan mothers used oral contraceptives (18).

Subfertility treatment

Subfertility itself is a known risk factor for preterm birth as In Vitro Fertilization (IVF) treatment transfer more than one embryo, and multiple gestations increase the risk of early birth (1). In this study, IVF percentage is very poor, i.e. two mothers (1.2%) aged 33 and 28 years underwent such treatment as they had not conceived for more than 3 years after the marriage, and delivered very preterm babies.

Multiple Pregnancies

Eleven multiple pregnancies [ten twins (11.6%) and one triplet (1.7%)) were recorded in this study. The mean and are range of mothers who delivered twins were 27.5 (±6.1) and 20- 37 years respectively, and 30% of them were above 30 years. The age of the mother who delivered triplets was 32 years. It might be due to multiple birth rates increase with increasing maternal age, i.e. more than 30 years (19). However all the multiple pregnancies (n=11) were terminated in moderate to late preterm, and none of them had IVF treatment.

Abortion and prior preterm delivery

The previous history of abortion also positively influences current preterm birth (10, 12), because of infectious conditions and vascular complications during pregnancy. (20). In this study, 17.3% of the mothers had previous history of abortion, and in a previous study it was 26.1% (21). Further association of preterm deliveries with the subsequent pregnancies had also been reported (12),

Previous caesarean section

All the mothers (n=17) who had past history of caesarean section delivered the current preterm baby by caesarean section. Among those, 5.9% delivered very preterm babies. Even though 13 (76.5%) mothers maintained inter-pregnancy interval of 1-3 years, mode of delivery was caesarean section, because of there is a risk of uterus rupture in case of trial of labour (22), and most of the mothers and their obstetricians in Sri Lanka would not be happy to take the risk (23). Further, few studies also reported that the history of the previous cesarean section positively had significant relationship with the incidence of preterm delivery (12, 22).

Intercourse during Pregnancy

More than half of the mothers (52.8%) reported that they had sexual intercourse during the last two weeks before the delivery, and 9.7% of them delivered very preterm babies. The reason for the risk of sexual intercourse on preterm delivery might be that the pregnant mothers may have more chances of getting infected with pathogenic microorganisms if they engage in frequent intercourse and have increased risk of preterm delivery (24). Hence, restriction of sexual intercourse is routinely recommended to prevent preterm labour (25). However, there is an evidence that sexual intercourse does not increase the risk of delivering preterm babies (26). So, it is contradictory to conclude that having sexual intercourse during the last two weeks before the delivery may lead to preterm delivery.

Pregnancy Complications

More than half of the mothers (54.9%) did not report pregnancy complications. It might be due to paying home visits and health education regarding pre-conception preparation and the prevention of pregnancy complications by Public Health Midwives (7). Among the pregnancy complications, pre rupture of membrane (46.3%) and

hypertension (24.2%) were in high incidence and they matched with a Sri Lankan study (27, 28). Among the mothers diagnosed with pregnancy complications, 10.3% of them only have delivered very preterm babies.

Frequency of mothers diagnosed with anemia was 9.2%, while the prevalence of anemia in pregnancy in Sri Lanka is 29.1% (29). However, in an Asian country, Pakistan, 93.0% of the mothers who delivered preterm babies were diagnosed with anemia (10). Further, underweight might be co-existed with anemia (7), and it is evidenced in this study that 37.5% of the anemic mothers were underweight

Influence of pregnancy conditions on preterm deliveries

Table 2 describes the influence of pregnancy conditions on very and moderate to late preterm deliveries. Eclampsia, pre-pregnancy diabetes mellitus, previous history of preterm birth, short inter pregnancy interval, and multiple gestations are associated with an increased risk of preterm birth (30).

Table 2: Relationship between pregnancy conditions of the mothers and the gestational age of the preterm babies.

Pregnancy Factors	Gestational Age				p- value	OR	95 % CI
	VP		MLP				
	No	%	No	%			
BMI category					0.351 (FET)	0.585	0.185-1.850
UW/ OW/ OB	9	7.0	120	93.0			
NW	5	11.4	39	88.6			
Parity					0.092 (FET)	3.021	0.909-1.038
Primi	10	12.2	72	87.8			
Not primi	4	4.4	87	95.6			
Pregnancy interval					1.000 (FET)	1.117	0.116-1.719
<1 year	1	6.2	15	93.8			
>1 year	4	5.6	67	94.4			
Contraceptive used					0.411 (FET)	0.578	0.174-1.924
Yes	4	5.8	65	94.2			
No	100	9.6	94	90.4			
Previous PTB					1.000 (FET)	0.986	0.207-4.694
Yes	2	8.0	23	92.0			
No	12	8.1	136	91.9			
Previous LSCS					1.000 (FET)	0.688	0.084-5.606
Yes	1	5.9	16	94.1			
No	13	8.3	143	97.1			
Pregnancy complications					0.407 (FET)	1.695	0.562-5.112
Yes	8	10.3	70	89.7			
No	6	6.3	89	93.7			
Sexual intercourse two weeks before delivery					0.578 (FET)	1.607	0.516-5.009
Yes	9	9.7	84	90.3			
No	6	30.0	14	70.0			

*FET- Fisher Exact Test value, *p<0.050 = statistically significant, VP- Very Preterm, MLP- Moderate to late preterm, UW- underweight, OW- overweight, OB- obesity, LSCS- lower segmental caesarean section, PTB- preterm birth*

Majority of the very preterm babies (9 babies out of 14 nos.) were delivered either by underweight or overweight or obese mothers. However, no statistically significant association was found between the gestation age of babies and the category of body mass index of the mothers (p= 0.351).

Among the primi mothers, majority (87.8%) of them delivered moderate to late preterm babies, and primi mothers were 3.021 times more likely to deliver very preterm babies. However, no statistically significant association was found between parity and gestation (p=0.092). Only one baby was born to the mother who maintained a short inter-pregnancy interval of <1 year, and it was 1.117 times risk to deliver very preterm. However, no statistically significant association was found between pregnancy interval and gestation age of preterm babies(p>0.050). Majority of the very preterm babies (n=10) were delivered by mothers who did not use contraceptives before the current pregnancy. However, the use of contraceptive methods did not influence the gestation (p= 0.411). The babies born to the mothers who underwent subfertility treatment were very preterm (n=1) and moderate to late preterm babies (n=1). None of the very preterm babies were twins or triplets, i.e. all the multiple pregnancies (n=11) were terminatedin moderate to late preterm.

Among the very preterm babies (n=14), two babies were born to the mothers who had previous history of preterm delivery, and one baby was born to the mother who has attended previous cesarean section. However, such previous histories of pregnancy records had no statistically significant association with the gestational age of the babies (p>0.050).

The majority of the very preterm babies (9 out of 14 nos.) were delivered by the mothers who had sexual intercourse during the last two weeks before delivery, and it had 1.607 times the risk to deliver very preterm babies. However, no significant association was found between sexual intercourse during the last two weeks before delivery and gestational age (p= 0.578). Among the very preterm babies (n=14), 8 babies were born to mothers who were diagnosed with pregnancy complications. It was 1.695 times the risk to deliver very preterm babies, however, no statistically significant association was observed between pregnancy complications and gestational age (p=0.407).

Conclusion

Risk factors causing very preterm delivery were by the mothers who were primies, maintained inter pregnancy interval of <1 year, had sexual intercourse before two weeks of delivery, and diagnosed with pregnancy complications. To arrive at a definite decision, preterm babies should be compared with term babies as well.

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Conflict of interests

Authors declare that they have no conflict of interests.

References

1. Menon R. Spontaneous preterm birth, a clinical dilemma: etiologic, pathophysiologic and genetic heterogeneities and racial disparity, Acta Obstet Gynecol Scand 2008; 87(6): 590-600. doi: 10.1080/00016340802005126. PMID: 18568457.

2. UN Inter-agency group for child mortality estimation, Mortality rate, under-5(per1,000livebirths, Available at: https://data.worldbank.org/Indicator/SH.DYN.MORT?end=2016&locations=LK&start=1975&view=chart, 2017 [Accessed 23 Oct. 2017].

3. Rosário EVN, Gomes MC, Brito M, Costa D. Determinants of maternal health care and birth outcome in the Dande Health and Demographic Surveillance System area, Angola, PLoS One 2019; 14(8): e0221280. Published 2019 Aug 22. doi:10.1371/journal.pone.0221280

4. Daniel WW. Biostatistics: a foundation for analysis in the health sciences. 7th Ed. New York: John Wiley & Sons. 1999

5. Kiridana V, Wickremasinghe N. An observational study on retinopathy of prematurity in the neonatal intensive care unit at Teaching Hospital, Peradeniya, Sri Lanka. Sri Lanka Journal of Child Health 2010; (39): 49. https://doi.org/10.4038/sljch.v39i2.1957.

6. Statistics Unit, Teaching Hospital, Jaffna, 2021.

7. Perera UAP, Assefa Y, Amilani U. Postnatal care coverage and its determinants in Sri Lanka: analysis of the 2016 demographic and health survey. BMC Pregnancy Childbirth 2021; 21, 299. https://doi.org/10.1186/s12884-021-03770-0.

8. Department of census and statistics. Demographic and Health Survey report. Colombo:Department of Census and Statistics; 2016. http://repo.statistics.gov.lk/handle/1/17.

9. Hollowell J, Oakley L, Kurinczuk JJ, Brocklehurst P, Gray R. The effectivenessof antenatal care programmes to reduce infant mortality and preterm birth in socially disadvantaged and vulnerable women in high-income countries: a systematic review, BioMed Central Pregnancy and Childbirth 2011; 11(13): p.1-20. https://doi.org/10.1186/1471-2393-11-13.

10. Shaikh K, Premji SS, Rose MS, Kazi A, Khowaja S, Tough S. The associationbetween parity, infant gender, higher level of paternal education and preterm birth in Pakistan: a cohort study, BioMedCentral Pregnancy and Childbirth 2011; 11: 88. doi:10.1186/1471-2393-11-88.

11. Girsen A, Mayo JA, Carmichael SL, Phibbs CS, Shachar BZ, Stevenson DK, Lyell DJ, Shaw GM, Gould JB. Women's prepregnancy underweight as a risk factor forpreterm birth: a retrospective study, British Journal of Obstetrics and Gynaecology 2016; 123 (12): p.2001- 2007.doi:10.1111/1471-0528.14027.

12. Di Renzo GC, Giardina I, Rosati A, Clerici G, Torricelli M, Petraglia F. Maternal Risk Factors for Preterm birth: A country- based population analysis, European Journalof Obstetrics Gynecology and Reproductive Biology 2011; 159(2): p.342-346. DOI: https://doi.org/10.1016/j.ejogrb.2011.09.024.

13. Family Health Bureau, Ministry of Health, Nutrition & Indigenous Medicine, Extraordinary gazette no. 1760/32 date 31.05.2012).

14. Bukair AZ, AI-Saqladi AWM, AI-Sadeeq AH. Interpregnancy interval and the risk of preterm birth: a case- control study of infants born at AI-Sadaqa General Teaching Hospital,Aden, Yemen, International Journal of Reproduction, Contraception, Obstetrics andGynecology 2016; 5 (4): p. 1181-1186. https://dx.doi.org/10.18203/2320-1770.ijrcog20160881.

15. Kamburova MS, Georgieva SL, UN M. Marital Status and Health of the Mother asRisk Factors for Premature Birth in Pleven, Bulgaria. International Journal of Health Administration and Education Congress 2016; 2: p.53-62. doi:10.12738/SM.2016.1.0014.

16. Rannan-Eliya RP, Wijemanne N, Liyanage IK, Jayanthan J, Dalpatadu S, Amarasinghe S, Anuranga C, The quality of outpatient primary care in public and private sectors in Sri Lanka—how well do patient perceptions match reality and what are the implications?, Health Policy and Planning 2015; 30 (1): i59–i74. Doi:10.1093/heapol/czu115.

17. Bloch JR, Webb DA, Mathew L, Culhane JF. Pregnancy intention and contraceptive use at six months postpartum among women with recent preterm delivery, Journalof Obstetetrics, Gynecology and Neonatal Nursing 2012; 41(3): p.389-397. doi: 10.1111/j.1552-6909.2012.01351.x.

18. Ruwanpathirana T, Fernando DN, Senanayake H. Antenatal morbidity experiencesand pregnancy outcome in a cohort of women – a community based study, Journal of the Collegeof Community Physicians of Sri Lanka 2014; 19 (1): pp.18–26. Doi:10.4038/jccpsl.v19il.7622.

19. Luke B, Brown MB. Contemporary risks of maternal morbidity and adverse outcomes with increasing maternal age and plurality. Fertility and sterility 2007; 88(2): 283–293. https://doi.org/10.1016/j.fertnstert.2006.11.008.

20. Moreau M, Kaminski P, Ancel Y Benoı JB. Previous induced abortions and the risk of very preterm delivery: results of the EPIPAGE study, An International Journal of Obstetrics and Gynaecology 2005; 112: p.430-437. doi: 10.1111/j.1471-0528.2004.00478.x.

21. Burguet A, Kaminski M, Abrahma-Lerat L, Schaal JP, Cambonie G, Fresson J, Grandjean H, Truffert P, Marpeau L, Voyer M, Roze JC, Treisser A, Larroque B. The complex relationship between smoking in pregnancy and very preterm delivery, British Journal of Obsterics and Gynecology 2004; 11(3): p. 258-265. https://doi.org/10.1046/j.1471-0528.2003.00037.x.

22. Williams CM, Asaolu I, Chavan NR, Williamson LH, Lewis AM, Beaven L, Ashfor KB. Previous cesarean delivery associated with subsequent preterm birth in the UnitedStates, European journal of Obstetrics, Gynecology and Reproductive Biology 2018; 229: p.88-93. https://doi.org/10.1111/1471-0528.16594.

23. Gunasekera PC, Wijesinghe PS, Goonewardene, IMR. The caesarean section rate is rising, CMJ 2001; 4 (4): 119-120.

24. Read JS, Klebanoff MA. Sexual intercourse during pregnancy and preterm delivery;effects of vaginal microorganisms. The Vaginal Infections and Prematurity Study Group. American Journal of Obsteterics and Gynecology 1993; 168(2): p. 514-519. https://doi.org/10.1016/0002-9378(93)90484-Z.

25. Jones C, Chan C, Farine D. Sex in pregnancy, Canadian Medical Association Journal 2011; 183 (7): p.815–818. DOI: https://doi.org/10.1503/cmaj.091580.

26. Sayle AE, Savitz DA, Throp JM, Hertz-Picciotto I, Wilcox AJ. Sexual activityduring late pregnancy and risk of preterm delivery, Obsteritics and Gynecology 2001; 97 (2): p.283- 289. https://doi.org/10.1016/S0029-7844(00)01147-9.

27. Wijayasundara WMSK, Gunathilaka KPP, Senavirathna HMS, De Silva BSS. Factors influencing low birth weight among babies born in the Teaching Hospital Anuradhapura: a preliminary study, The Open University of Sri Lanka, Annual Academic Sessions 2013; p. 189-192.

28. Madala VRK, Keshav Gangadharan K, Shivaraju P, Mateti DP. Prevalence of teenage pregnancy and its obstetric and perinatal outcomes in a rural tertiary care hospital. Int J Reprod Contracept Obstet Gynecol 2020; 9: 3989-93. DOI: 10.18203/2320-1770.ijrcog20204005.

29. Family Health Bureau, Ministry of Health, 2020. https://fhb.health.gov.lk/index.php/en/.

30. Behrman RE, Butler AS, Institute of Medicine (US) Committee on Understanding Premature Birth and Assuring Healthy Outcomes; Preterm Birth: Causes, Consequences, and Prevention. Washington (DC): National Academies Press (US); 2007. 5, Medical and Pregnancy Conditions Associated with Preterm Birth. Available from: https://www.ncbi.nlm.nih.gov/books/NBK11363/