Effect of interpregnancy interval on risk of spontaneous preterm birth in Emirati[*] women, United Arab Emirates

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Objective To investigate whether a short interpregnancy interval is a risk factor for preterm birth in Emirati women, where there is a wide range of interpregnancy intervals and uniformity in potentially confounding factors.

Methods A case-control design based on medical records was used. A case was defined as a healthy multiparous Emirati woman delivering a healthy singleton spontaneously before 37 weeks of gestation between 1997 and 2000, and a control was defined as the next eligible similar woman delivering after 37 weeks of gestation. Women were excluded if there was no information available about their most recent previous pregnancy or if it had resulted in a multiple or preterm birth. Data collected from charts and delivery room records were analysed using the STATA statistical package. All variables found to be valid, stable and significant by univariate analysis were included in multivariate logistic regression analysis.

Findings There were 128 cases who met the eligibility criteria; 128 controls were selected. Short interpregnancy intervals were significantly associated with case status ($P<0.05$). The multivariate adjusted odds ratios for the 1st, 2nd, and 4th quartiles of interpregnancy interval compared with the lowest-risk 3rd quartile were 8.2, 5.4, and 2.0 (95% confidence intervals: 3.5–19.2, 2.4–12.6, and 0.9–4.5 respectively).

Conclusion A short interpregnancy interval is a risk factor for spontaneous preterm birth in Emirati women. The magnitude of the risk and the risk gradient between exposure quartiles suggest that the risk factor is causal and that its modification would reduce the risk of preterm birth.

Keywords Birth intervals; Labor, Premature/etiology; Causality; Risk factors; Confounding factors (Epidemiology); Case-control studies; United Arab Emirates (*source: MeSH, NLM*).

Mots clés Intervalle entre naissances; Accouchement prématuré/étiologie; Causalité; Facteur risque; Facteurs de confusion (Epidémiologie); Etude cas-témoins; Emirats arabes unis (*source: MeSH, INSERM*).

Palabras clave Intervalo entre nacimientos; Trabajo de parto prematuro/etiología; Causalidad; Factores de riesgo; Factores de confusión (Epidemiología); Estudios de casos y controles; Emiratos Árabes Unidos (*fuente: DeCS, BIREME*).

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Introduction

Preterm birth is the single most important cause of perinatal mortality in North America and Europe (*1*). In addition, it is responsible for nearly half of all cases of congenital neurological disability, including cerebral palsy (*2*). Most of the affected babies have lifelong impairment and impose a significant economic burden on society. The primary prevention of preterm birth is therefore a major public health goal.

The identification of modifiable causal factors is an essential first step in any primary prevention programme. A short interpregnancy interval has been identified as potentially being such a risk factor but the results of epidemiological studies have been equivocal. Most were conducted in the USA using large administrative data sets (*3–11*) or large cohorts assembled for research purposes (*12, 13*), and found that a short interpregnancy interval was significantly related to an increased risk of preterm birth; however, the relative risks or odds ratios were 2 or less (*3, 4, 6, 8–11*). Some studies have found no significant relationship (*5, 7, 12, 13*). Similar results have been obtained in two studies in other countries (*14, 15*). Since most large data sets contain limited information on potential confounders, the findings of such studies could well be affected by confounding. Only one study excluded iatrogenic preterm births (*12*), only one excluded births of infants with congenital anomalies (*15*), and none excluded births to mothers with chronic medical conditions or obstetric complications, although all of these types of preterm birth could arise from an etiological pathway differing from those of most preterm births.

Recent studies in Denmark (*16*) and India (*17*) provided more convincing evidence of a possible causal relationship. More detail was available to control for possible confounders, the odds ratios were larger (3.6 and 2.7 respectively for very short interpregnancy intervals), and there was a risk gradient between very short and short interpregnancy intervals. However, each of these studies was conducted in a heterogeneous population and only a limited number of potential confounders could be identified and controlled for in the analysis. Also, iatrogenic preterm births, births involving congenital anomalies, and births to mothers with chronic disease or obstetric complications were not excluded.

We are unaware of any previous research on the relationship between interpregnancy interval and preterm birth in Emirati women. Our objective was to identify the relationship between interpregnancy interval and spontaneous preterm birth in a homogeneous population of healthy mothers delivering healthy babies and to control for as many potential confounders as possible in order to improve sensitivity and increase confidence that any significant relationship found was not attributable to confounding.

The study was carried out in Al Ain, United Arab Emirates, a small desert city served by three hospitals in which 99% of all deliveries occur. The general population is heterogeneous, consisting of Emirati people and expatriates from many countries. However, within this population, the citizens of the United Arab Emirates, readily identifiable from health records, are homogeneous. Most maintain their traditional Arab and Islamic culture while using the services of the modern health care system. Smoking and the use of alcohol are uncommon among women. All women who delivered are married and have reasonable socioeconomic status and access to health care (*18*). According to a survey conducted in 1995, the total fertility rate was 4.9 (*18*). Large families are not universal and there is a wide range of interpregnancy intervals.

Approval for the study was obtained from the Research Ethics Committee of the Faculty of Medicine and Health Sciences, United Arab Emirates University.

Methods

Case definition

A case was defined as a healthy multiparous Emirati woman with no obstetric complications who gave birth spontaneously to a healthy singleton before the beginning of the 37th week of pregnancy, as documented in delivery room records. The estimate of gestational age was based on all available evidence at the time of birth, including the prenatal record, using an algorithm that included the date of last menstrual period and ultrasound results. We defined a healthy mother as one who had no significant chronic disease such as diabetes, hypertension, or renal disease, and a healthy infant as one with a five-minute Apgar score >5 (or born healthy before arrival at hospital) and with no observed congenital defects.

The delivery room records of all three hospitals in Al Ain for 1997–2000 were searched in order to identify women who met the case definition. These women's inpatient charts were examined to determine whether they met two additional eligibility criteria: the most recent previous pregnancy resulted in the birth, after 36 completed weeks of pregnancy, of a healthy (as defined above) singleton in the same hospital; and

no use of infertility clinic services for either the current or previous pregnancy. The women who met all the eligibility criteria became cases. For each case, the control was the next woman in the delivery room record who fulfilled all the eligibility criteria except that the birth occurred after 37 completed weeks of gestation.

Data collection

Data on cases and controls were collected from the chart and the delivery room records. Some women sought prenatal care at outlying clinics and only came to the hospital prenatal clinics in late pregnancy. The records that they brought with them were used by the hospital clinic and delivery room staff to estimate gestational age. However, these records did not become part of the hospital records and therefore could not be accessed for this study. Furthermore, data on several potential confounders in these women, such as smoking and socioeconomic status, were unavailable in the medical records.

The mean interbirth interval was calculated as the time between the first birth and the birth of the most recent previous child divided by the number of birth intervals in that time (i.e. by gravidity minus two). No mean interbirth interval was calculated for mothers whose gravidity was <4. The current interpregnancy interval was calculated as the interval between the birth of the most recent previous child and the birth of the current child minus the gestational age of the current child as documented at the time of delivery.

Data analysis

The data were analysed using the STATA statistical package. Cases and controls were assessed for comparability on all the variables collected. The probability of the differences between cases and controls occurring by chance was tested by means of the Wilcoxon rank sum test for continuous variables and by χ^2 test for categorical variables. The two-tailed test was considered significant if $P<0.05$. All variables considered to be valid and found to be significant by univariate analysis were included in multivariate logistic regression analysis. Variables were considered significant on multivariate analysis if the 95% confidence interval of the adjusted odds ratios did not include 1.

Results

The eligibility criteria for inclusion as cases were fulfilled by 128 women; 128 eligible controls were selected. Table 1 and Table 2 indicate the results of the univariate analysis for all the variables of interest.

It was felt that the number of prenatal visits was artificially reduced for cases because of their earlier delivery, so this variable was discarded. The maternal weight at the first prenatal visit was discarded as the women who did not plan to appear for this visit at the hospital clinic until late in pregnancy and who delivered early were less likely to appear and have a weight recorded. This left an artificial preponderance of first visits in late pregnancy, with their heavier weights, in the control group. The birth weight of the current baby was also discarded as being too unstable because of its close association with case or control status: the 90th percentile of the weights of cases overlapped the 10th percentile of the weights of controls. The remaining variables found to be significantly associated with case/control status on univariate analysis (gestational age of the most recent previous baby, a previous preterm birth, and current interpregnancy

Table 1. **Distribution of continuous variables by case/control status**

Variable	Cases		Controls	
	Median	**No. of cases with valid data**	**Median**	**No. of controls with valid data**
No. of prenatal visits[a]	3 (2–4)[b]	113	4 (3–6)	113
Maternal age (years)	27.6 (22.7–31.7)	128	27.7 (24.0–34.5)	128
Maternal height (cm)	154 (152–158)	73	155 (152–159)	74
Maternal weight at first prenatal visit (kg)[a]	62.7 (53.5–71.0)	113	67.6 (59.0–78.5)	125
Maternal haemoglobin level at first prenatal visit (g/100 ml)	10.8 (10.1–11.8)	76	11.1 (10.4–11.9)	85
Maternal gravidity	4.5 (3–7)	128	5 (3–8)	128
Gestational age of current baby (weeks)[a]	35 (34–36)	128	40 (39–40)	128
Gestational age of most recent previous baby (weeks)[a]	39 (38–40)	125	40 (39–40)	128
One-minute Apgar score of current baby	8 (8–9)	126	8 (8–9)	127
One-minute Apgar score of previous baby	8 (8–8)	121	8 (8–9)	123
Birth weight of current baby (g)[a]	2565 (2215–2880)	128	3300 (3050–3573)	128
Mean interbirth interval (months)	21.5 (15.7–27.7)	77	19.6 (16.5–26.7)	87
Current interpregnancy interval (months)[a]	12.4 (7.9–21.2)	128	19.1 (13.1–25.5)	128

[a] Cases and controls differ significantly ($P<0.05$) by Wilcoxon rank sum test.
[b] Figures in parentheses are interquartile ranges.

Table 2. **Distribution of categorical variables by case/control status**

Variable	% of cases with valid data	% of controls with valid data
Ultrasound report available	85 (128)[b]	91 [128][c]
At least 1 prenatal visit[a]	88 (128)	98 [128]
Previous preterm birth[a]	23 (123)	7 [126]
Current baby male	52 (128)	53 [128]
Most recent previous baby male	51 (128)	54 [128]

[a] Cases and controls differ significantly ($P<0.05$ by χ^2 test).
[b] Figures in parentheses are numbers of cases with valid data.
[c] Figures in square brackets are numbers of controls with valid data.

interval) were entered into the multivariate logistic regression. The results of both the univariate and the multivariate logistic regression analysis are given in Table 3. The unadjusted odds ratios for the 1st, 2nd and 4th quartiles of interpregnancy interval compared with the lowest-risk 3rd quartile were 5.8, 4.0, and 1.6 respectively. The corresponding multivariate adjusted odds ratios were 8.2, 5.4, and 2.0. The gestational age of the most recent previous baby remained significant in the multivariate model ($P = 0.00$ and 0.09 for the two categories analysed) as did previous preterm birth ($P = 0.00$).

Discussion

A highly significant relationship between short interpregnancy interval and spontaneous preterm birth was demonstrated in what was a very homogeneous population, after as many confounders as possible were controlled for through both study design and analysis. This relationship was stronger than those reported in previous studies (*3, 4, 6, 8–11, 14–17*). A risk gradient was evident in that the shortest interval quartile displayed a higher risk than the second quartile compared to the lowest-risk third quartile. This suggests that a short interpregnancy interval is a causal risk factor for spontaneous preterm birth and that it is a stronger risk factor than previously observed. Attenuation of the odds ratios in previous studies may have been attributable to uncontrolled confounding in heterogeneous populations.

Notwithstanding efforts to remove prematurity in the most recent previous delivery as a confounder by requiring that this delivery be full term, i.e. after more than 36 weeks, residual confounding was identified for this variable.

This study had several weaknesses. There was no information available on potentially important confounders such as maternal smoking status, socioeconomic status, and access to health care. However these factors are remarkably homogeneous in Emirati women in Al Ain. In a recent anonymous survey of 200 Emirati women in Al Ain aged 18 to 36 years, none reported smoking or alcohol consumption (*19*). There is a fairly wide range of family income among Emirati people in Al Ain. However, the social safety net guarantees that every Emirati person has access to good medical care free of charge, except for a small annual fee, and that they have the amenities necessary to support healthy living (*20*). Furthermore, only 17% of women in the region under study participate in the workforce, another potentially unidentified confounding variable (*21*).

A case-control study design has inherent weaknesses. In particular there is difficulty in controlling selection biases and confounding variables. These problems can only be overcome by carrying out a cohort study. However, odds ratios of the magnitude of those found in the present study give some confidence in the validity of the findings. The study was very small, and consequently the odds ratios had wide confidence

Table 3. **Effects of current interpregnancy interval on case/control status according to logistic regression**

Current interpregnancy interval (months)	Unadjusted odds ratio $n = 256$	Adjusted odds ratio[a] $n = 246$	P-value of adjusted odds ratio
Quartile 1: 2.8–8.9	5.8 (2.7–12.7)[b]	8.2 (3.5–19.2)	0.00
Quartile 2: 9.0–15.9	4.0 (1.9–8.4)	5.4 (2.4–12.6)	0.00
Quartile 3: 16.0–22.9	1.0	1.0	–
Quartile 4: 23.0–82.7	1.6 (0.7–3.2)	2.0 (0.9–4.5)	0.10

[a] Adjusted simultaneously for gestational age of the most recent previous baby, previous preterm birth, and current interpregnancy interval by multivariate logistic regression analysis (10 women were excluded from this analysis due to missing data for at least one of the variables in the model).
[b] Figures in parentheses are 95% confidence intervals.

intervals. A larger study would probably have produced narrower confidence intervals. However, such a study would be unlikely to find a substantially different magnitude for the odds ratios.

Some studies have found that a long interpregnancy interval is also a risk factor for preterm birth (*3, 4, 6, 11, 15, 17*) We did not find a significant risk for the 4th quartile of interpregnancy interval compared to the 3rd quartile (*P* = 0.10). The risk may have been attenuated in our study since only 11% of women in the 4th quartile had a sufficiently long interpregnancy interval, i.e. over 36 months, to be at risk according to these previous studies.

One study suggested that preterm infants with intrauterine growth retardation should be removed from the analysis of the effect of the interpregnancy interval on preterm birth (*10*). This could not be done in this study since no standards for birth weight in relation to gestational age have been developed in the United Arab Emirates. However, if the standards for infants born at sea level of Caucasian women in the USA are used (*3*), no case or control infant in our study was affected by intrauterine growth retardation.

Our findings, in conjunction with those of other studies on the relationship between the interpregnancy interval and preterm birth, strongly suggest that a short interpregnancy interval is a causal factor for spontaneous preterm birth. The evaluation of the outcomes of primary prevention programmes based on this putative causal factor would resolve the matter. ■

Résumé

Effet de l'intervalle intergestationnel sur le risque d'accouchement prématuré spontané chez les ressortissantes des Emirats arabes unis

Objectif Rechercher si un intervalle intergestationnel court constitue un facteur de risque d'accouchement prématuré chez les ressortissantes des Emirats arabes unis, où l'intervalle entre les grossesses est très variable et où les facteurs de confusion potentiels sont uniformes.

Méthodes Un schéma d'étude cas-témoins reposant sur les dossiers médicaux a été adopté. Le cas était défini comme étant une ressortissante des Emirats arabes unis multipare, en bonne santé, ayant accouché spontanément d'un nouveau-né unique, en bonne santé, avant 37 semaines de grossesse entre 1997 et 2000 dans les Emirats arabes unis, et le témoin comme la parturiente suivante sur le registre, répondant aux mêmes critères et ayant accouché après 37 semaines de grossesse. Les femmes étaient exclues de l'étude si on ne disposait pas d'informations sur leur précédente grossesse ou si celle-ci avait abouti à une naissance multiple ou à un accouchement prématuré. Les données recueillies d'après les dossiers médicaux et les registres des salles d'accouchement ont été analysées au moyen du logiciel de statistique STATA. Toutes les variables trouvées valables, stables et significatives lors de l'analyse univariée ont été incluses dans une analyse de régression logistique multivariée.

Résultats L'étude a porté sur 128 cas répondant aux critères et 128 témoins. Les intervalles intergestationnels courts étaient significativement associés au statut de cas (p<0,05). Les odds ratios ajustés issus de l'étude multivariée pour les premier, deuxième et quatrième quartiles de l'intervalle intergestationnel par rapport au troisième quartile correspondant au risque le plus faible étaient respectivement de 8,2 (intervalle de confiance (IC) à 95 % : 3,5-19,2), 5,4 (IC 95 % : 2,4-12,6) et 2,0 (IC 95 % : 0,9-4,5).

Conclusion Un intervalle intergestationnel court constitue un facteur de risque d'accouchement prématuré spontané chez les ressortissantes des Emirats arabes unis. La valeur du risque et sa progression d'un quartile d'exposition à l'autre laissent à penser qu'il s'agit d'un facteur causal et qu'en le modifiant, il serait possible de réduire le risque d'accouchement prématuré.

Resumen

Efecto del intervalo entre embarazos en el riesgo de parto prematuro espontáneo entre las mujeres de los Emiratos Árabes Unidos

Objetivo Investigar si un intervalo breve entre embarazos es un factor de riesgo de nacimiento prematuro en las mujeres de los Emiratos Árabes Unidos, entre las cuales coexisten una gran diversidad de intervalos entre embarazos y unos mismos factores de confusión potenciales.

Métodos Se utilizó un diseño de casos y controles basado en los registros médicos. Los casos se definieron como toda mujer multípara sana que daba a luz a un solo niño espontáneamente antes de las 37 semanas de gestación entre 1997 y 2000, y los testigos como la siguiente mujer elegible que tenía un niño después

de las 37 semanas de gestación. Se excluyó a las mujeres sobre las que no había ninguna información disponible acerca de su embarazo anterior más reciente, o en las que éste había concluido con un parto múltiple o prematuro. Los datos recopilados a partir de gráficos y de registros de la sala de partos se analizaron utilizando el paquete estadístico STATA. Todas las variables válidas, estables y significativas según el análisis con una sola variable se incluyeron en el análisis de regresión logística multifactorial.

Resultados Se observó una frecuencia significativamente mayor ($P < 0,05$) de intervalos cortos entre embarazos en la muestra de casos. Las razones de posibilidades (OR) ajustadas arrojadas por el estudio multifactorial para los cuartiles 1º, 2º y 4º del intervalo entre embarazos, comparados con el tercer cuartil (el de menor riesgo), fueron de 8,2, 5,4 y 2,0, respectivamente (intervalos de confianza del 95%: 3,5–19,2, 2,4–12,6 y 0,9–4,5).

Conclusión Un intervalo corto entre embarazos es un factor de riesgo de nacimiento prematuro espontáneo entre las mujeres de los Emiratos Árabes Unidos. La magnitud del riesgo y el gradiente de riesgo entre los cuartiles de exposición llevan a pensar que se trata de un factor de riesgo causal y que su prolongación reduciría el riesgo de parto prematuro.

References

1. Berkowitz GS, Papiernik E. Epidemiology of preterm birth. *Epidemiologic Reviews* 1993;15:414-43.
2. Goldenberg RL, Rouse DJ. Prevention of premature birth. *New England Journal of Medicine* 1998;339:313-20.
3. Adams MM, Delaney KM, Stupp PW, McCarthy BJ, Rawlings JS. The relationship of interpregnancy interval to infant birthweight and length of gestation among low-risk women, Georgia. *Paediatric and Perinatal Epidemiology* 1997;11 Suppl 1:48-62.
4. Zhu BP, Rolfs RT, Nangle BE, Horan JM. Effect of the interval between pregnancies on perinatal outcomes. *New England Journal of Medicine* 1999;340:589-94.
5. Ekwo EE, Moawad A. The relationship of interpregnancy interval to the risk of preterm births to black and white women. *International Journal of Epidemiology* 1998;27:68-73.
6. Kallan JE. Reexamination of interpregnancy intervals and subsequent birth outcomes: evidence from U.S. linked birth/infant death records. *Social Biology* 1997;44:205-12.
7. Kallan JE. Effects of interpregnancy intervals on preterm birth, intrauterine growth retardation, and fetal loss. *Social Biology* 1992;39:231-45.
8. Shults RA, Arndt V, Olshan AF, Martin CF, Royce RA. Effects of short interpregnancy intervals on small-for-gestational age and preterm births. *Epidemiology* 1999;10:250-4.
9. Khoshnood B, Lee KS, Wall S, Hsieh HL, Mittendorf R. Short interpregnancy intervals and the risk of adverse birth outcomes among five racial/ethnic groups in the United States. *American Journal of Epidemiology* 1998;148:798-805.
10. Klerman LV, Cliver SP, Goldenberg RL. The impact of short interpregnancy intervals on pregnancy outcomes in a low-income population. *American Journal of Public Health* 1998;88:1182-5.
11. Fuentes-Afflick E, Hessol NA. Interpregnancy interval and the risk of premature infants. *Obstetrics and Gynecology* 2000;95:383-90.
12. Lang JM, Lieberman E, Ryan KJ, Monson RR. Interpregnancy interval and risk of preterm labor. *American Journal of Epidemiology* 1990;132:304-9.
13. Brody DJ, Bracken MB. Short interpregnancy interval: a risk factor for low birthweight. *American Journal of Perinatology* 1987;4:50-4.
14. Ferraz EM, Gray RH, Fleming PL, Maia TM. Interpregnancy interval and low birth weight: findings from a case-control study. *American Journal of Epidemiology* 1988;128:1111-6.
15. Cnattingius S, Granath F, Petersson G, Harlow BL. The influence of gestational age and smoking habits on the risk of subsequent preterm deliveries. *New England Journal of Medicine* 1999;341:943-8.
16. Basso O, Olsen J, Knudsen LB, Christensen K. Low birth weight and preterm birth after short interpregnancy intervals. *American Journal of Obstetrics and Gynecology* 1998;178:259-63.
17. Mavalankar DV, Gray RH, Trivedi CR. Risk factors for preterm and term low birthweight in Ahmedabad, India. *International Journal of Epidemiology* 1992;21:263-72.
18. Al-Quassimi S, Fikri M, Farid S, editors. *United Arab Emirates family health survey 1995*. Riyadh: Ministry of Health Abu Dhabi and Council of Health Ministers of Gulf Cooperation Council States; 1996.
19. Saadi H, Reed R, Carter AO, Qazaq H, Al Suhaili AR. Bone density estimates and assessment of risk factors for osteoporosis in young women. *Eastern Mediterranean Health Journal.* In press 2001.
20. *Annual statistical abstract.* 19th ed. Abu Dhabi: Ministry of Planning; 1994.
21. *United Arab Emirates in figures 97/1998.* Abu Dhabi: Ministry of Planning; 1999.