Investigation of the risk factors of preterm birth and infant mortality in Hungary – epidemiological and cost-effectiveness analyses

Ph.D. Thesis

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This thesis is based on the following papers:

[I]   **Csaba Nyári**, Tibor András Nyári, Richard J.Q, McNally. Trends in infant mortality rates in Hungary between 1963 and 2012. Acta Paediatrica, (In press) IF:1.842

[II]   Nyári T, **Nyári C**, Woodward M, Mészáros G, Deák J, Nagy E, Kovács L. Screening for *Chlamydia trachomatis* in asymptomatic women in Hungary. An epidemiological and cost-effectiveness analysis. Acta Obstet Gynecol Scand. 2001;80:300-306.IF: 1.206

Other publications of the candidate related to the thesis

[I]   Nyári Tibor, Deák Judit, **Nyári Csaba**, Mészáros Gyula. Epidemiological investigation of the frequency of *Chlamydia trachomatis* infection and its risk factor [A *Chlamydia trachomatis* fertőzés gyakorisága és lehetséges rizikófaktorainak meghatározás epidemiológiai módszerekkel.] XXI. Neumann Kollokvium Veszprém, 1998 pp 167-169. (in Hungarian)

[II]   **Nyári Csaba**, Nyári Tibor. Investigation of cyclic trends using logistic regression [Ciklikus trendek vizsgálata logisztikus regresszióval.] XXVII. Neumann Kollokvium Szeged, 2014: pp 63-66.ISBN 978-963-369-040-0 (in Hungarian)

[III]   **Nyári Csaba**, Nyári Tibor. Investigation of risk factors of stillbirth in Hungary [A késői magzati halálozás kockázati tényezőinek vizsgálata Magyarországon.] XXVII. Neumann Kollokvium Szeged, 2014: pp 149-152. ISBN 978-963-369-040-0 (in Hungarian)

Introduction

According to the World Health Organization, the global number of deaths in the first year of life was 4.6 million, in 2013. The global infant mortality rate was 31.7 per 1,000 live births in 2013 [1]. About five times higher infant mortality was observed in Africa (60 per 1,000 live births) than in Europe (11 per 1,000 live births) [1]. An infant mortality of 4.6 per 1,000 live births was reported in Hungary in 2013 [1]..

Preterm birth (based on less than 37 completed weeks of gestation) is one of the most significant problems in perinatology. Beck et al [2] reported that the World Health Organization estimated that 9.6% births worldwide were preterm in 2005 which translated into about 12,9 million births definable as preterm. Furthermore, about 0.5 million (6.2%) and 8,198 (8.4%) births were preterm in Europe and Hungary in 2005, respectively [2].

Various infections including *Chlamydia trachomatis* could cause preterm birth. In pregnancy, *Chlamydia trachomatis (C. trachomatis)* may cause a wide range of serious complications, which include premature delivery, post-partum endometritis, ophthalmia neonatorum and neonatal pneumonia [8]. Furthermore, *C. trachomatis* is a major cause of neonatal morbidity and mortality [9-10]. *Chlamydial* infections of the genital tract are a problem worldwide. Despite the fact that chlamydial infection is relatively rare, the rate of genital chlamydial infection has increased in Hungary, since 2006 [3].

In this thesis, we present two epidemiological studies investigating i) the infant mortality in Hungary and ii) the role of maternal Chlamydia trachomatis in preterm birth.

Trends in infant mortality rates in Hungary between 1963 and 2012 (Study I)

Introduction

Infant mortality rates have decreased in developed countries over the last two decades, including Hungary. Infant mortality has been investigated in several countries and certain risk factors, including socio-economic, geographic and environmental, have been implicated. [4]. In a recent paper, the Hungarian infant mortality rate of 4.6 per 1,000 live births in 2013 was slightly lower than the Central European average of 5.6 per 1,000 live births per year, but was higher than the reported Western European average of 3.2 per 1,000 live births [1]. In spite of these annual reported trends in Hungarian infant mortality, rates have not yet been investigated in any detail.

Aims

- In the longitudinal study, changes in infant mortality rates, annual trends and the effect of some possible risk factors related to deaths under the age of one year were investigated during the 50-year interval between 1 January 1963 and 31 December 2012, in Hungary.

- Furthermore, seasonality analyses of cyclic trends in infant mortality rates, were also carried out.

Methods

Infant death was defined as death after live birth and before the age of one year. Data on the numbers of live births and infant deaths were obtained from the published nationwide population register of the Hungarian Central Statistical Office [3]. Annual birth and infant death data were available, with birth weight, sex, maternal age and maternal education, for both live births and infant death cases throughout the full 50-year period. Complete information was available for birth weight and sex. Maternal age was also categorised using younger or older than 35-years-of-age. Maternal education was categorised as no primary school attended, primary school attended, vocational or secondary grammar school attended and higher education, which was regarded as the default group in the risk analyses. A birth weight of less than 2,500 g was regarded as a low birth weight. The infant mortality rate was calculated as the number of infant deaths divided by the number of live births and expressed per 1,000 births.

The negative binomial regression method was applied to investigate the trends across annual rates and investigate the effect of possible risk factors - low birth weight, maternal education and sex – in relation to infant mortality. Relative risks (RR) and 95% confidence intervals (95% CIs) were calculated.

Data on the month of the death were aggregated over the study period. Cyclic trends in these monthly data were investigated using the Walter-Elwood method [6] and the logistic regression method using both sine and cosine functions [5].

All analyses were performed using STATA Software version 9.0 (Stata Corp LP, College Station, Texas, USA)

Results

During the 50-year interval, there were 6,336,976 live births (3,247,936 boys and 3,089,040 girls) and 136,537 infant deaths (77,751 boys and 58,786 girls) in Hungary. There were 47,055 (34.5%) within the first 24 hours of delivery, 87,757 (64.3%) during the early neonatal period.

The annual infant mortality rate declined by 88.6% from the maximum of 42.9 per 1,000 births in 1963 to the minimum of 4.9 per 1,000 births in 2012. There was a significant RR trend per annum of 0.954 (95% CI 0.953–0.955; p<0.001). A similar decreasing trend was detected for the annual rate of early neonatal deaths with an annual RR of 0.944 (95% CI 0.941–0.948; p<0.001).

A significantly increased risk of infant mortality was found in boys, with an RR of 1.23 (95% CI 1.19-1.28, p<0.001), than girls. The highest risk of infant mortality with an RR of 20.2 (95% CI 19.9–20.4 p<0.001) was observed in the low birth weight group compared with the normal birth weight group. A significantly increased risk of infant death with an RR of 1.73 (95% CI: 1.64 , 1.83; p<0.001) was found in mothers over the age of 35 compared to mothers under this age. Nevertheless, the risk of an infant's death was higher in mothers with lower levels of education than those with higher levels of education (RR=1.31, 95% CI 1.30-1.32, P<0.001).

A significant cyclic trend in all infant mortality was revealed by the logistic regression model, with a peak of deaths during late February (p<0.001). Similarly, a significant cyclic trend was found with a peak of deaths during March in the group of cases who died during the early neonatal period (p<0.001), respectively. In double peak models neither the sine nor cosine variables were significant for all infants. However a significant (p=0.045) double peak in May and November was detected in the group of cases who died during the early neonatal period.

Conclusion

In this study, a number of risk factors and trends were investigated in relation to infant mortality using well established statistical methods. We found seasonal effects related to infant and early neonatal mortality, with peaks in February and March we might speculate that the significant peak of neonatal and infant mortality could be related to respiratory infections at the end of winter. These findings could prove useful in preventive strategies, but further cohort studies should be carried out to investigate this hypothesis using detailed individual data.

Chlamydia trachomatis infection and the risk of perinatal mortality and a cost-effectiveness study (Study II)

Introduction

The eye disease trachoma, described five thousand years ago in China, is the earliest known human disease entity caused by Chlamydiae.. Trachoma was known by the ancient Greeks and Romans. In humans, the syndromes caused by C. trachomatis fall into three groups, each of which tends to be associated with a particular set of serotypes:

- trachoma (mainly serotypes A, B, Ba and C)
- oculogenital and, occasionally, more general infections (mainly serotypes D-K, although serovar B has been recovered from both genital disease and endemic trachoma) and
- lymphogranuloma venereum (serotypes L1, L2, L2a and L3).

C. trachomatis infection is an STD that is common worldwide and have surpassed gonorrhoea as the number one in the United States (USA), the United Kingdom and the Scandinavian countries

Epidemiological evidence indicates that chlamydial infections of the genital tract are a global problem. The 35-45% of women have cervical chlamydial infection. Furthermore, Chlamydial infection of the cervix is found in 15-30% of women attending clinics for sexually transmitted diseases (STD). Chlamydial infections of the genital tract do not invariably cause symptoms that would prompt a person to seek medical aid [8]. Delayed treatment of untreated asymptomatic infection increases the risk of transmission to sex partners and sequelae, including endometritis and salpingitis in women, resulting in spontaneous abortion, premature delivery, tubal infertility and ectopic pregnancy. Neonates delivered vaginally from infected mothers may contract chlamydial conjunctivitis or pneumonia. Therefore, identification and treatment of infected persons is important not only for the individuals but also to prevent the spread of *C. trachomatis* in the society. Screening asymptomatic women for chlamydial infection is the cornerstone of effort to reduce the burden of the disease, since chlamydial cervicitis is not associated with specific complaint [9]. The rate of genital chlamydial infection has increased in most of the European countries including Hungary [10].

AIMS

- To characterize the role of *C. trachomatis* in preterm birth, a cross-sectional multicenter survey was carried out in order to determine the prevalence and risk factors of *C. trachomatis* infection in the population of asymptomatic women.
- A cost-effectiveness analysis of chlamydial infection screening and its sequelae was carried out, to aid in developing screening criteria for genital chlamydial infection in young women aged under 20 years, in Hungary.

Methods

The cross-sectional study started and terminated in 1995 in five different centers in three regions of Hungary: Western Hungary (Szombathely); Middle Hungary (Budapest and Szeged); Eastern Hungary (Miskolc and Nyíregyháza). The ELISA and the non-amplified nucleic acid hybridization methods (PACE 2 Gen-Probe) were applied for the examination of *C. trachomatis*.

An incremental cost-effectiveness analysis [11] was performed to compare the strategies of screening with the ELISA method (the sensitivity and specificity of this test are 70% and 99%, respectively) for the detection of *C. trachomatis* (strategy A), screening with use of the amplified Gen-Probe method (the sensitivity and specificity of this test are 92% and 99%, respectively)] for the detection of *C. trachomatis* (strategy B), and no application of screening methods (strategy C). Costs were based on local charges of the Hungarian Health Insurance.

Results

Accordingly, a total of 1,300 pregnant women were examined for the occurrence of *C. trachomatis*. The overall average *C. trachomatis* infection rate was found to be 4.5% (n=59), the data varying in the range 1.5-6.8% between the regions. The group aged under 20 years displayed a very high rate of infection (12.6%). Certain potential risk factors relating to the infection were examined. A young age, an unmarried status (single or divorced) and the regional difference (there was only a 1.5% rate of chlamydial infection in Western Hungary where the rate of unemployment has been lowest during the early 1990s) proved to be statistically significant predictors of the infection.

The most cost-effective strategy was strategy A (screening for *C. trachomatis* by using the ELISA method). The policy of strategy B (screening for *C. trachomatis* by using Gen-Probe method) was less cost-effective than neither testing nor treating (strategy C), unless certain conditions were satisfied. If the costs of the diagnostic test were less than or equal to 2,500 HUF, or if the prevalence of infection in women were greater than 16.7%, screening strategy B would be more cost-effective than neither testing nor treating.

As compared with no screening, strategy B (screening for *C. trachomatis* by using Gen-Probe method) involved an extra cost of approximately $221 for each case prevented, but prevented an additional 10,000 more cases relative to strategy A (screening for *C. trachomatis* by using the ELISA method).

Conclusions

We conclude that age-based screening (women aged 15-19 years) with amplified Gen-Probe assays (combined with treatment of positive patients and partner notification) is the preferred screening strategy for women in Hungary. Furthermore, extension of the screening procedure to test all pregnant women for diseases that can be transmitted transplacentally or perinatally comprises an important part of obstetrical care.

The introduction of the screening of *C. trachomatis* can reduce the sequelae of untreated *C. trachomatis* infections and can detect other STDs. This prevention may reduce the number of expensive diagnostic and therapeutic methods

KEY NOTES

- This study investigated annual and seasonal death trends for infants of less than one-year-of-age in Hungary from 1963-2012.

- The highest risk of infant mortality with an RR of 20.2 (95% CI 19.9–20.4 p<0.001) was observed in the low birth weight group compared with the normal birth weight group.

- Annual infant mortality declined significantly during the study period and significantly increased in the low birth weight and lower maternal education groups.

- A significant cyclic trend in mortality was revealed, with a peak in deaths in late winter for all infants and peaks in May and November for early neonatal infants.

- Young age, unmarried status (single or divorced) and region proved to be statistically significant predictors of the genital chlamydial infection.

- Age-based screening with amplified Gen-Probe assays (combined with treatment of positive patients and partners) is the preferred screening strategy of *Chlamydia trachomatis* for women in Hungary.

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