

Screening for group B *Streptococcus* in pregnant women: a systematic review and meta-analysis

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Infection with Group B *Streptococcus* (GBS) is considered an important public health problem. It is associated with: Neonatal sepsis, meningitis, pneumonia, neonatal death, septic abortion, chorioamnionitis, endometritis and other perinatal infections. The aim of this study was to determine the best screening strategy for GBS in pregnant women. For this a systematic review and meta-analysis were carried out in the Nursing Department of the Federal University of São Paulo, Cochrane Center, Brazil. Sources used were, EMBASE, LILACS, Medline, list of references, personal communication and the Cochrane library. The criterion for the selection of the studies was; studies which analyze some type of screening for GBS in pregnant women. Independent of the comparator, all analyses were in favor of a universal screening program for reducing the incidence of neonatal sepsis. The evidence obtained in this study suggests that the strategy of universal screening of pregnant women associated with the use of prophylactic antibiotics is safe and effective.

Descriptors: Pregnant Women; *Streptococcus agalactiae*; Meta-Analysis.

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Rastreamento de *Streptococcus* do grupo B em gestantes: revisão sistemática e metanálise

A infecção por *Streptococcus* do grupo B (GBS) é considerada importante problema de saúde pública. Está associada à sepse neonatal, meningite, pneumonia, óbito neonatal, aborto séptico, coriomnionite, endometrite e outras infecções perinatais. O objetivo deste estudo foi determinar a melhor estratégia de rastreamento de GBS em gestantes. Como método usou-se a revisão sistemática com metanálise. A pesquisa foi realizada no Departamento de Enfermagem/Universidade Federal de São Paulo/Centro Cochrane do Brasil. Para a busca usaram-se as fontes Embase, LILACS, MEDLINE, lista de referências bibliográficas, comunicação pessoal e Cochrane Library. Usaram-se, como critério de seleção, os estudos que analisaram algum tipo de rastreamento para GBS em gestantes. Independente do comparador, os resultados apontam que todas as análises foram favoráveis ao programa de screening universal para a redução da incidência de sepse neonatal. Pode-se concluir que evidências obtidas no estudo são sugestivas de que a estratégia de screening universal para as gestantes, associada ao uso de antibiótico profilático, é segura e efetiva.

Descritores: Gestantes; *Streptococcus agalactiae*; Metanálise.

Rastreo de *Streptococcus* del grupo B en gestantes: revisión sistemática y metanálisis

La infección por *Streptococcus* del grupo B (GBS) es considerada un importante problema de salud pública. Los estreptococos están asociados a: sepsis neonatal, meningitis, neumonía, muerte neonatal, aborto séptico, corioamnionitis, endometritis y otras infecciones perinatales. El objetivo del estudio fue determinar la mejor estrategia de rastreo de GBS en gestantes. Se trata de una revisión Sistemática con Metanálisis. Fue realizada en el Departamento de Enfermería de la Universidad Federal de Sao Paulo, Centro Cochrane de Brasil. Se utilizaron las siguientes fuentes: EMBASE, LILACS, Medline, lista de referencias bibliográficas, comunicación personal y Cochrane Library. Como criterio para la selección de los estudios, se escogieron los que analizaron algún tipo de rastreo para GBS en gestantes. Independientemente del comparador, todos los análisis fueron favorables al programa de screening universal para la reducción de la incidencia de sepsis neonatal. Las evidencias obtenidas en el estudio sugieren que la estrategia de screening universal para las gestantes asociado al uso de antibióticos profilácticos es segura y efectiva.

Descritores: Mujeres Embarazadas; *Streptococcus agalactiae*; Metanálisis.

Introduction

Streptococcus agalactiae or group B *Streptococcus* (GBS) was more important for veterinary medicine in the past, as the causal pathogen for bovine mastitis, however, in 1938 GBS was identified as a human pathogen, related to three fatal cases of puerperal sepsis⁽¹⁾. With the first published study of perinatal GBS

infection, the relationship of the bacteria with negative maternal and neonatal outcomes became clear and its importance in diseases related to human beings was recognized, especially in the perinatal period⁽²⁾. It is currently considered a serious infection, being one of the major causes of meningitis, pneumonia,

neonatal sepsis, neonatal death, septic abortion, chorioamnionitis, endometritis, pyelonephritis, cellulitis, puerperal sepsis, and premature rupture of membranes, among other perinatal infections⁽³⁻⁵⁾. This problem aroused the interest of health authorities so that, in 1996, the Center for Disease Control (CDC) published a report concerning standards and recommendations, from the public health perspective, for prevention of perinatal diseases caused by *Streptococcus agalactiae* with support from the American College of Obstetricians and Gynecologists, the American Academy of Pediatrics and other agencies⁽³⁾. In the guidelines two alternatives are suggested for prophylaxis in intrapartum pregnant women for the prevention of early neonatal infection by GBS. One based on the results of cultures of vaginal and anorectal content collected in the third trimester of pregnancy and the other based on the risk factors presented by the pregnant woman. The risk factors described are: Preterm labor <37 weeks of gestation, prior GBS bacteriuria, fever, prolonged rupture of membrane ≥ 18 hours, and the reporting of neonatal infection in previous a birth.

The guidelines were revised in 2002 and underwent some modifications based on evidence reported in some cases where vertical infection by GBS was detected where the pregnant woman did not present risk factors⁽⁴⁾. The latest update, of 2010, is based on the existing evidence of perinatal GBS prevention and reinforces the universal screening recommendations in the third trimester of pregnancy, standardizes the laboratory methods for detection of GBS, changes the dose of antimicrobial prophylaxis and updates the recommendations for premature infants and neonates at risk of early infection⁽⁵⁾. The main measure for the prevention of neonatal infection by group B *Streptococcus* is to identify and to prophylactically treat pregnant women, avoiding postpartum problems and early neonatal infection⁽⁶⁻⁷⁾.

There is intense debate concerning prevention strategies for perinatal GBS, with regard to the feasibility and impact of the protocols suggested by the CDC (based on risk factors or the universal screening of pregnant women), so that many countries still do not have defined policies to remedy the problem. The principle aim of this study is to identify the best strategy for prenatal screening for prevention of perinatal infection caused by GBS, having as the main premise to analyze the best strategy to identify pregnant women

infected/colonized by this bacterium who should be submitted to intrapartum prophylaxis, thus being more effective in reducing the incidence of neonatal sepsis. Motivated by the importance of the infection in the public health context, lack of standardization of preventive strategies and doubts about their effectiveness, this Systematic Review and Meta-analysis was performed in an unprecedented manner with support from the Department of Nursing / UNIFESP and the Cochrane Centre of Brazil.

Method

This Systematic Review and Meta-analysis followed the steps proposed by the Cochrane Collaboration⁽⁸⁾. Studies were included regardless of language or form of publication. As inclusion criterion, in this Meta-analysis it was necessary for the studies to present at least the primary outcome: Incidence of early neonatal sepsis, with the participants being pregnant women evaluated in the last trimester of pregnancy. The interventions compared for Meta-analysis were: screening based on maternal risk factors, universal screening or no preventive intervention for GBS. The exclusion criteria were studies that did not evaluate outcomes relevant to the study or which selected pregnant women in the first two trimesters of pregnancy.

Strategies for identification of the studies

The relevant studies were identified through electronic search of the Cochrane Library database, including the databases Cochrane Controlled Trials Register contained in the Cochrane Library 2010, volume 10, PUBMED (January 1966 to Jan 2010), EMBASE (January 1985 to Jan 2010), LILACS (January 1982 to Jan 2010), and SciELO (June 1998 to Jan 2010): www.controlledtrials.com, abstracts of work presented at conferences, published and identified references of review articles and of systematic reviews and identified references of randomized clinical trials. The main descriptors used in the search strategy were: "Mass Screening" OR "Neonatal Screening" OR screening AND *Streptococcus* group B OR *Streptococcus agalactiae*

Selection of the studies

The studies were read by two independent reviewers (MT) and (HS) in order to ascertain whether they met the inclusion criteria. The evaluation, by the reviewers, of the titles and abstracts of all identified

studies were not blind and complete copies of all the relevant articles were made available. In case of doubt or disagreement, a third reviewer (DAB) was asked to give an opinion regarding whether the study should be included or not.

Evaluation of the methodological quality

The methodological quality was defined as the confidence that the design and reporting of the study were free from bias⁽⁹⁾. Two independent reviewers used the STROBE (strengthening the reporting of observational studies in epidemiology) recommendations⁽¹⁰⁾. Based on the STROBE recommendations, the evaluation of this meta-analysis was divided into three categories: A - in the cases of the studies that fulfill 80% or more of the criteria; B - in the cases of compliance with between 80% and 50% of the criteria; and C - if there was less than 50% compliance with the criteria established by STROBE.

Data extraction and statistical analysis

The studies were initially stratified according

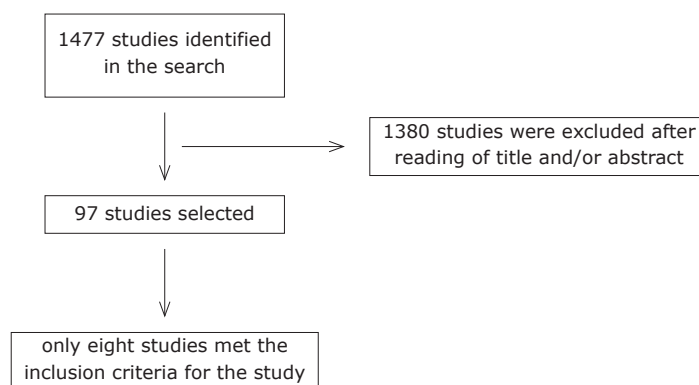


Figure 1 - Flowchart of the selection and identification of the studies

Finally, eight studies were included in this review: Gibbs et al.⁽¹²⁾, Hafner et al.⁽¹³⁾; Jeffrey et al.⁽¹⁴⁾; Main et al.⁽¹⁵⁾; Reisner et al.⁽¹⁶⁾; Vergani et al.⁽¹⁷⁾; Puopolo et al.⁽¹⁸⁾; Renner et al.⁽¹⁹⁾, as described in Figure 2.

Title	Author(s)	Year / Country	Study design	Interventions	Outcomes	STROBE
Neonatal Group B Streptococcal Sepsis during two years of a universal screening program	Gibbs RS, McDuffie RS, Jr, McNabb F, Fryer GE, Miyoshi T, Merenstein G.	1994 / USA	Retrospective cohort	Universal screening versus no intervention	Incidence of neonatal sepsis Experimental = 5/4843 Control = 10/6667	A
Group B streptococci during pregnancy: A comparison of two screening and treatment protocols.	Hafner E, Sterniste W, Rosen A, Schuchter K, Plattner M, et al.	1998 / Austria	Prospective cohort	Universal screening versus risk factor based screening	Incidence of neonatal sepsis Experimental = 0/3952 Control = 20/3700	A

(Figure 2 continue in the next page...)

(continuation)

Title	Author(s)	Year / Country	Study design	Interventions	Outcomes	STROBE
Eight-year outcome of universal screening and intrapartum antibiotics for maternal group B <i>Streptococcus</i> carriers.	Jeffrey HE, Lahra MM.	1998 / Australia	Prospective cohort	Universal screening versus no intervention	Incidence of neonatal sepsis: Experimental = 8/36342 Control = 8/5732	A
Prevention of early-onset invasive neonatal group B streptococcal disease in a private hospital setting: the superiority of culture-based protocols.	Main EK, Slagle T.	2000 / USA	Prospective cohort	Universal screening versus risk factor based screening	Incidence of neonatal sepsis: Experimental = 0/9304 Control = 15/13270	A
Performance of a group B streptococcal prophylaxis protocol combining high-risk treatment and low-risk screening.	Reisner DP, Haas MJ, Zingheim RW, Williams MA, Luthy DA	2000 / USA	Prospective cohort	Universal screening versus risk factor based screening	Incidence of neonatal sepsis Experimental = 2/9932 Control = 9/8188	B
Impact of different prevention strategies on neonatal group B streptococcal disease.	Vergani P, Patanè L, Colombo C, Borroni C, Giltri G, Ghidini A et al.	2002 / Italy	Retrospective cohort	Universal screening versus risk factor based screening	Incidence of neonatal sepsis: Experimental = 0.4/1000 Control = 0.8/1000	B
Early-onset group B streptococcal disease in the maternal screening.	Puopolo KM, Madoff LC, Eichenwald EC.	2005 / USA	Retrospective cohort (10 years)	Universal screening versus risk factor based screening	Incidence of neonatal sepsis Experimental = 0.37/1000 Control = 1.1/1000	B
Efficacy of a strategy to prevent neonatal early-onset group B streptococcus (GBS) sepsis.	Renner RM, Renner A, Schmid S, Hoesli I, Nars P, Holzgreve W.	2006 / Switzerland	Retrospective cohort (12 years)	Universal screening versus no intervention	Incidence of neonatal sepsis: Experimental = 0.53/1000 Control = 1/1000	A

Figure 2 - Summary of the characteristics of the included studies

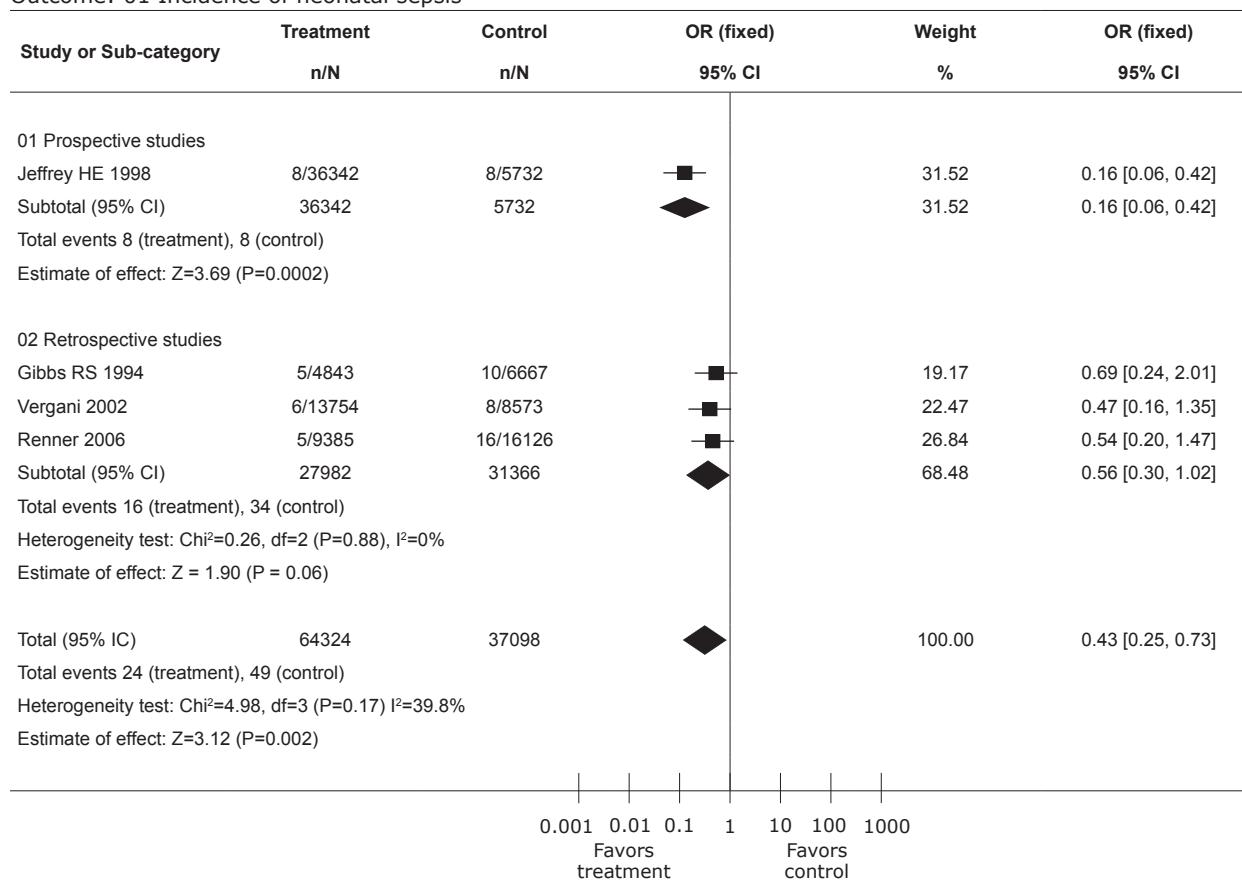
The studies included in Figures 3 and 4 addressed the incidence of neonatal sepsis caused by GBS; the figures are divided by type of intervention and design. The study by Jeffrey et al.⁽¹⁴⁾ of a prospective nature showed an incidence of sepsis of 0.2/1000 births for those patients who followed the universal screening protocol and of 1.4/1000 births for the risk factors based screening group. Regarding the retrospective cohort studies included in Figure 2, the incidence of each study were: Gibbs et al.⁽¹²⁾ 1/1000 births; Vergani et al.⁽¹⁷⁾ 0.4/1000 births; Renner et al.⁽¹⁹⁾ 0.5/1000 births for the groups of patients who underwent universal screening. The incidence of sepsis in the groups without preventive intervention (no screening) were: Gibbs et al.⁽¹²⁾ 1.5/1000 births; Vergani et al.⁽¹⁷⁾ 0.9/1000 births; Renner et al.⁽¹⁹⁾ 1/1000 births.

For the evaluation of the incidence of neonatal sepsis in Figure 2, four studies were included comparing universal screening with no screening, having n=64324 in the intervention group and n=37098 in the control group. The data show significant differences between the comparison groups, with a higher proportion of patients benefiting from universal screening, compared with the control group (no screening), with odds ratio of 0.43 (95% confidence interval of 0.25 to 0.73, p=0.002). It was not possible to identify substantial heterogeneity (statistically significant) among the included studies ($I^2=39.8\%$, p=0.17). However, the differences between the comparison groups were not statistically significant for the retrospective studies, as shown by the confidence intervals (horizontal lines) that intersect the line of the null hypothesis (vertical line).

Review: Strategy for the prevention of early neonatal infections

Comparison: 01 universal screening for the detection of GBS in pregnant women versus the control group of no screening

Outcome: 01 Incidence of neonatal sepsis



GBS=Group B *Streptococcus*

OR=Odds Ratio

CI=Confidence interval

n/N=Number of participants that expressed the event / Total number of participants of the group

Figure 3 - Odds ratio for incidence of neonatal sepsis: universal screening versus control (no screening)

Figure 4 shows significant superiority for the universal screening group versus the control group (risk factor based) when compared to the incidence of neonatal sepsis with an odds ratio of 0.22 (95% confidence interval of 0.14 to 0.34, $p=0.000001$). Heterogeneity was not identified among the included studies ($I^2=39.3\%$, $p=0.16$).

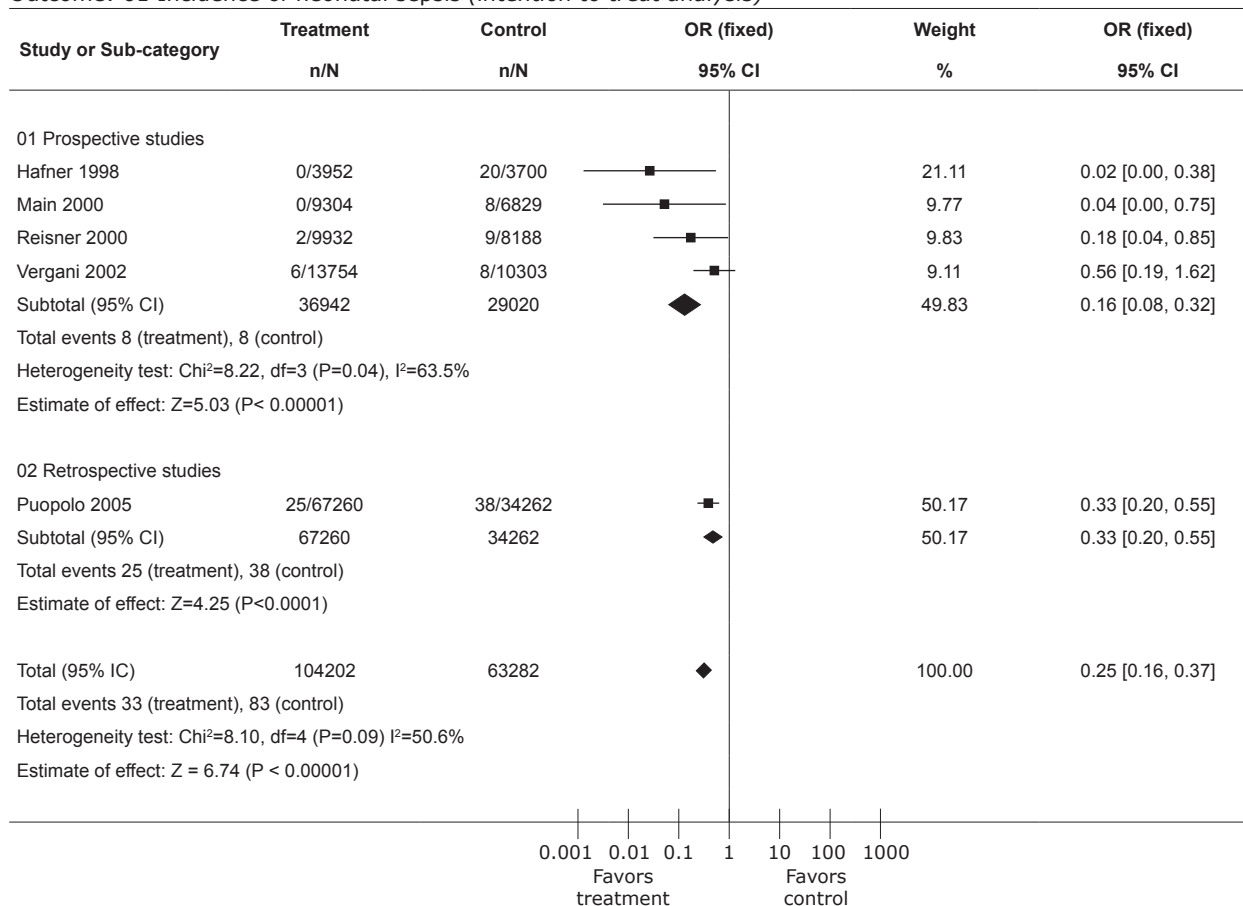
The methodology of this Systematic Review and

Meta-analysis rigorously followed the recommendations of the Cochrane and the STROBE, the entire process was performed by two independent reviewers, the search strategy was broad, there was no language restriction, and the studies included were evaluated regarding their methodological content. All these steps were intended to reduce the possibility of biases and to give more credibility to the results.

Review: Strategy for the prevention of early neonatal infections

Comparison: 02 universal screening for the detection of GBS in pregnant women versus the control group of risk factor based screening

Outcome: 01 Incidence of neonatal sepsis (*intention to treat analysis*)



GBS=Group B *Streptococcus*

OR=Odds Ratio

CI=Confidence interval

n/N=Number of participants that expressed the event / Total number of participants of the group

Figure 4 - Odds ratio for incidence of neonatal sepsis (analysis by protocol): Universal screening versus control group with risk factor based screening

Discussion

Data found in a large study that evaluated the impact of the implementation of the two CDC guidelines of 1996, based on risk factors, and 2002, suggesting universal screening, highlight the decline in the rates of neonatal GBS infection of approximately 0.47/1000 births in the period 1999 to 2001 to 0.34/1000 in 2004, consolidating the strategy of universal screening⁽²⁰⁻²³⁾. The fatality rate in neonates in the 1970's, a time when GBS had been recognized as a human pathogen, was approximately 50%⁽⁴⁾. However, with advances in neonatal care and increased use of prophylactic antibiotics, this rate decreased to 10-15% in the 1990's⁽²²⁻²⁵⁾ and to 5% after the introduction of measures of screening, prevention and prophylaxis for GBS^(5,21).

The impact on the reduction of the incidence of GBS in neonates is based on the timely detection of the bacteria in pregnant women, at between 35-37 weeks of gestation, by vaginal and rectal contents culture. The detection interval was stipulated because it is believed that colonization/infection may be transient and it is relevant to know the colonization/infection status in the period just prior to the birth. One study found that the predictive value was between 95%-98% for the women who were examined up to 5 weeks prior to delivery, but for those that were examined with a larger interval there was a decline in the predictive value⁽²⁶⁾. Another extremely important factor regarding the reduction of negative outcomes in neonates is the administration of intrapartum antimicrobial prophylaxis⁽⁶⁾. The efficacy of the use of penicillin and ampicillin intravenously in the intrapartum

period to prevent early neonatal infection caused by GBS has been demonstrated in clinical trials^(6,27).

Motivated by the relevance of the problem in the public health context the Municipal Health Secretariat of São Paulo State released a technical note for the screening for GBS in all pregnant women included in the Mãe Paulistana Program, in which the responsibilities are divided between the Primary Healthcare, to identify the pathogen at the appropriate time, the Maternity Unit to treat the pregnant women and the Neonatologist to prevent possible negative outcomes in the neonate⁽²⁸⁾. A recent analysis on the profile of deaths in children under one year of age in the municipality of São Paulo between 2000-2008, shows that diseases acquired in the perinatal period accounted for 57.8% in 2000 and 55.1% in 2008, this decline may reflect the actions of public policies on the prevention of and attention to neonatal infection caused by GBS⁽²⁹⁾.

Over time many advances have been seen in the prevention of this infection, however, there is a need for integrated actions for the implementation of screening protocols, prophylaxis and monitoring of the incidence of sepsis. In a cross-sectional study where the objective was to evaluate, by means of indicators established by the Ministry of Health⁽³⁰⁾, the quality of prenatal care offered in 12 primary health units of the municipality of São Paulo, showed that in the year 2000 none of the services analyzed were considered to be Excellent and only 7.7% of the services received this indicator in 2004⁽³¹⁾.

Implications for the practice

The evidence obtained in this study suggests that the strategy of universal screening for pregnant women associated with the use of prophylactic antibiotics is safe and effective, as demonstrated by the reductions in the incidence of neonatal sepsis.

Implications for research

- National studies to evaluate the magnitude of the problem of early neonatal infection caused by GBS in the maintenance of the mortality rate in the population;
- Studies which evaluate the impact of the adoption of preventive measures in Brazil,
- Prevention and prophylaxis alternatives for preterm infants.

Conclusion

Considering the first proposition and the unprecedented nature of this study in evaluating the

effectiveness of the screening strategies for GBS and the impact on reducing the incidence of neonatal sepsis, the superiority was clear of the universal screening strategy for the detection of GBS in sufficient time for the adoption of prophylactic measures.

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