Postęp w opiece perinatalnej w oparciu o metody poparte dowodami naukowymi

(Improvement in perinatal care due to evidence based medicine)

Janusz Gadzinowski
on behalf of the EPICE research group

NEONATUS 2016
29-30 września 2016r.
Effective Perinatal Intensive Care in Europe: Translating knowledge into evidence-based practice
Population-based prospective cohort in 2011/2012 with follow-up at 2 years. Data from medical charts. Parental questionnaire at 2 years.

Maternity and Neonatal Unit Study. Unit characteristics and use of interventions sent to head of unit.
Very preterm infants

- Very preterm births (< 32 weeks of gestation) are 1-2% of all births but half of all perinatal deaths.
- Medical advances for these infants improved their survival dramatically in past decades.
- High risks of long term motor and neurological impairment.

How can better organization of care and use of evidence-based medical practices improve outcomes?
Results

• Cohort study
  – 10 329 total births
  – 7 901 Live births
  
  Gestational age: 28.4 (2.4)
  Birthweight: 1196 (426)
  Male: 54.1%

• Unit study (Neonatal units ≥ 10 very preterm admissions and associated maternity units)
  – 134 neonatal units
  – 123 maternity units
N of live births by region

FR: IDF
UK: Yorkshire and Humb
BE: Flanders
DE: Hesse
IT: Lazio
UK: East Mid
IT: Emilia
PT: Lisbon
UK: Northern
NL: East Central
DK: Eastern
PL: Wielkopolska
FR: Northern
PT: Northern
SE: Stockholm
Estonia
DE: Saarland
IT: Marche
FR: Burgundy
Average GA in EU regions

Medium = 28.5
% GA< 26 weeks

- BE:Flanders: 11
- DE:Hesse: 18
- DE:Saarland: 13
- DK:Eastern: 13
- Estonia: 10
- FR:Burgundy: 8
- FR:IDF: 9
- FR:Northern: 9
- IT: Emilia: 12
- IT:Lazio: 14
- IT:Marche: 8
- NL:East-Central: 14
- PL:Wielkopolska: 19
- PT:Lisbon: 11
- PT:Northern: 9
- SE:Stockholm: 17
- UK: East Mid: 13
- UK: Northern: 16
- UK: Yorkshire: 11
Multiple pregnancies

Child<32 GA admitted to neonatal ward
Severe congenital anomalies

• The diagnosis of severe congenital defect
  - Eurocat classification adopted for determining severe birth defects, for example: anomalies associated with a high mortality
TOP caused by congenital anomalies (% of MOSAIC cohort database - 22-31 GA)

Papiernik E. et. al. BJOG, 2008, 361-368.
Severe congenital anomalies, live discharge
TOP caused by CA and its impact to neonatal deaths (22-31 t.c.)

Papiernik E. et. al. BJOG, 2008, 361-368.

Neonatal deaths due to CAs
Neonatal deaths associated with CAs

BE Flanders
DK Eastern
FR Ille-de-France
DK Eastern
BE Flanders

0,6%
0,2%
1,7%
0,6%
2,2%
1,7%
4,6%
3,3%
2,3%
1,9%
2,6%
1,3%
6,8%
3,8%
2,5%
2,1%
2,2%
2,0%
1,5%
1,3%
2,2%
0,9%
0,2%
1,3%
1,5%
1,9%
1,3%
1,7%
1,7%
1,8%
2,8%
3,6%
Morbidity of newborn admitted to NICU in Wielkopolska region

<table>
<thead>
<tr>
<th>Condition</th>
<th>MOSAIC</th>
<th>EPICE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=361</td>
<td>N=306</td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>IVH grade II or IV</td>
<td>77</td>
<td>21,3</td>
</tr>
<tr>
<td>Surgery for NEC</td>
<td>9</td>
<td>2,5</td>
</tr>
<tr>
<td>Surgery for PDA</td>
<td>11</td>
<td>3,0</td>
</tr>
<tr>
<td>Cryocoagulation or laser treatment for ROP</td>
<td>26</td>
<td>7,2</td>
</tr>
<tr>
<td>Receiving oxygen (BPD)</td>
<td>33</td>
<td>9,1</td>
</tr>
</tbody>
</table>
In-hospital mortality after live birth

<table>
<thead>
<tr>
<th>Region</th>
<th>2003</th>
<th>2011/12</th>
</tr>
</thead>
<tbody>
<tr>
<td>BE:Flanders</td>
<td>14%</td>
<td>14%</td>
</tr>
<tr>
<td>DE:Hesse</td>
<td>12%</td>
<td>11%</td>
</tr>
<tr>
<td>DK:Eastern</td>
<td>18%</td>
<td>13%</td>
</tr>
<tr>
<td>FR:IDF</td>
<td>16%</td>
<td>19%</td>
</tr>
<tr>
<td>IT:Lazio</td>
<td>21%</td>
<td>23%</td>
</tr>
<tr>
<td>NL:East-Central</td>
<td>13%</td>
<td>16%</td>
</tr>
<tr>
<td>PL:Wielkopolska</td>
<td>35%</td>
<td>21%</td>
</tr>
<tr>
<td>PT:Northern</td>
<td>14%</td>
<td>14%</td>
</tr>
<tr>
<td>UK: Northern</td>
<td>16%</td>
<td>16%</td>
</tr>
<tr>
<td>UK: Trent?East Mid</td>
<td>10%</td>
<td>10%</td>
</tr>
<tr>
<td>Total</td>
<td>14%</td>
<td>19%</td>
</tr>
</tbody>
</table>
Mortality in Wielkopolska region (22-31 GA)

- 96.5% in 1988
- 96.5% in 1998
- 82.1% in 2003
- 75.0% in 2011/12
- 75.0% in MOSAIC
- 57.6% in EPICE

% of in-hospital mortality rate by gestational age:
- <25 weeks
- 26-27 weeks
- 28-29 weeks
- 30-31 weeks

- Twarowska, I., Kornacka MK., i wsp.
- 2003 - MOSAIC
- 2011/12 - EPICE
Changes in survival, live births
Wielkopolska, Poland - EPICE

2003  MOSAIC
2011/12  EPICE
Diagnosis of CP and severe morbidity, follow-up sample

Number of obs = 16
Spearman's rho = 0.5251
Test of Ho: c7p and snm_all_p are independent
Prob > |t| = 0.0368
• To improve perinatal care in Poland, we need a good perinatal statistics program, like at INSERM in Paris. This will help to identify courses of action.

• Alternatively, joining to the VON (Vermont Oxford Network)
Very preterm infants

• Very preterm births (< 32 weeks of gestation) are 1 to 2% of all births, but up to half of perinatal deaths
• Medical advances for these infants improved their survival dramatically in past decades
• High risks of long term motor and neurological impairment

How can use of evidence-based medical practices improve outcomes?
Evidence based care for very preterm infants

• Implementation of evidence-based guidelines may be a cost effective approach to improving quality of care

• Uptake of evidence based practices can improve outcomes in NICU (Kilbride et al. Pediatrics 2003; Wirtschafter et al. Pediatrics 2011)

• Showing that interventions are effective is not enough; Interventions must be translated into clinical settings – regulatory, organisational, cultural and personal factors constrain adoption (Cabana et al. JAMA 1999; Grol et al. Lancet 2003).

→ Little research about how scientific knowledge is implemented in the care of very preterm infants in Europe
Objectives

To improve very preterm outcomes by ensuring that medical knowledge is translated into effective perinatal care

1. **Build an empirical knowledge base about how scientific evidence is translated into health service provision in maternity and neonatal units by**
   - measuring the use of key medical interventions in clinical settings
   - identifying factors favouring adoption of evidence-based practices
   - providing information on the effectiveness of medical practices

2. **Identify catalysts for the uptake of evidence-based practices**

3. **Develop strategies to achieve change** with the participation of front-line clinicians, researchers and policy makers.
Study design

Case studies
Regional governance institutions and policies

Cohort Study

Unit Study

Qualitative studies
decision-making in units
Methods – EPICE cohort

• **Type of study**: prospective cohort study
• **Study population**: births 22 +0 to 31 +6 weeks including TOPs and fetal deaths in 2011/2012
• **Follow-up**: until death or discharge from hospital, and then at corrected age 2 years.
• **Data** on medical practices, clinical and socio-demographic characteristics and health outcomes
• **Data collection**: from medical records using standardised instrument and definitions
• **Completeness**: inclusions cross-checked with birth registries in maternity units and using other data when possible (civil registration)
Potentially preventable very preterm mortality and morbidity: an All-or-None analysis of 4 evidence-based practices in the European EPICE cohort
Use of evidence based practices to improve survival without severe morbidity for very preterm infants: results from the EPICE population based cohort

Jennifer Zeitlin, Bradley N Manktelow, Aurelie Piedvache, Marina Cuttini, Elaine Boyle, Arno van Heijst, Janusz Gadzinowski, Patrick Van Reempts, Lene Huusom, Tom Weber, Stephan Schmidt, Henrique Barros, Dominico Dillalo, Lis Toome, Mikael Norman, Beatrice Blondel, Mercedes Bonet, Elisabeth S Draper, Rolf F Maier

ABSTRACT

OBJECTIVES
To evaluate the implementation of four high evidence practices for the care of very preterm infants to assess their use and impact in routine clinical practice and whether they constitute a driver for reducing mortality and neonatal morbidity.

RESULTS
outcomes were in-hospital mortality, severe neonatal morbidity at discharge, and a composite measure of death or severe morbidity, or both. We modelled associations using risk ratios, with propensity score weighting to account for potential confounding bias. Analyses were adjusted for clustering within delivery hospital.
Objectives

• Investigate the use of evidence-based practices in the EPICE cohort

• Measure the impact of non-use of these practices on outcome (and thus possible margin for improvement)

• Assess whether use of these practices contributes to differences between regions in Euroupe
All or none approach

Measures use of all selected interventions for eligible patients

Advantages
• more closely reflects the interests and likely desires of patients
• fosters a system perspective
• offers a more sensitive scale for assessing improvements

Measures
• The number of measures in the set should be small (4 to 8)
• Each one should measure performance with respect to the specified elements of good care
• Each of the care elements should be supported by evidence that links it to one or more desirable end points

T Nolan, DM Berwick. All-or-None Measurement Raises the Bar on Performance. JAMA
Selection of interventions

4 of 17 interventions

Widely accepted with high level of evidence

Linked to mortality or short term morbidity

1. Delivery in tertiary centres
2. Antibiotics for PPROM **
3. Tocolysis **
4. Administration of antenatal corticosteroids
5. Magnesium sulphate - neuroprotective intervention
6. Delivery by caesarean section
7. Time (early or late) for cord clamping **
8. Management of hypothermia
9. Surfactant Replacement Therapy
10. Inhaled NO
11. Breastfeeding
12. Management of patent ductus arteriosus (PDA) ***
13. Developmental Care/Kangaroo care (skin-to-skin) **
14. BPD prevention strategies (vitamin A/Caffeine) **
15. Postnatal corticosteroids (non use)
16. ROP screening and treatment

** in unit study only
*** in cohort study only
## Interventions selected for this analysis

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Indicator</th>
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</table>
| Delivery in maternity unit with appropriate onsite neonatal care            | ➢ Delivery in a maternity unit with on-site neonatal unit admitting at least 20 VPTI/year  
➢ For babies <28 weeks, delivery in a maternity unit with neonatal unit admitting at least 30 VPTI/year |
| Use of antenatal corticosteroids                                           | ➢ Received any ANS between 24 and 31 weeks                                                                                                                                                                |
| Prevention of hypothermia                                                   | ➢ Temperature ≥36 at admission to NICU                                                                                                                                                                    |
| Surfactant use                                                              | For infants born below 28 weeks GA  
➢ Surfactant within 2 hours  OR  
➢ Early CPAP                                                                    |
Cohort study

• **Total inclusions:**
  – 10,329 total births
  – 7,900 live births

• **Study population:** all infants without severe congenital anomalies admitted to neonatal care (N=7,514) and survivors to discharge home (N=6,792).
Methods

Outcome variables
In-hospital mortality: death before discharge home from hospital after live birth.

Composite variable for severe neonatal morbidity
• Intraventricular hemorrhage (IVH) Papille grades III-IV
• Cystic periventricular leukomalacia (cPVL)
• Surgery/peritoneal drainage for necrotizing enterocolitis (NEC)
• Retinopathy of prematurity (stages >=3).

Independent variables
• Receipt of each evidence-based practice, if eligible
• Composite variable
  – EB Care: Received all 4 EB practices, given eligibility
  – Non-EB Care: Did not receive all 4 EB practices, given eligibility
Methods

• **Co-variables**
  – Gestational age, sex, multiplicity, SGA, pregnancy complications (PPROM, hypertensive disorders of pregnancy)
  – Organizational factors: delivery on same day as admission

• **Analysis**
  – Exploration of clinical factors associated with non-use of EB
  – Multi-level hierarchical models (patients, units) to assess impact of non-use of EB on outcomes
  – Use of propensity scores to control for confounding
  – Prediction of impact of 100% use of EB care
Receipt of four evidence-based interventions

- Place of delivery: 88.2%
- Antenatal steroids: 89.2%
- Hypothermia management: 74.4%
- Surfactant or early CPAP (<28 weeks GA): 83.0%
- All interventions: 58.3%
The chances of receiving full evidence based care was lower for infants less than 26 weeks’ gestation, infants who were small for their gestational age, and infants with a low Apgar score.
Receipt of EB practices by region

[Bar chart showing the receipt of EB practices by region, with regions listed on the x-axis and the percentage on the y-axis.]

- BE:Flanders
- DK:Eastern
- Estonia
- FR:Northern
- FR:Burgundy
- FR:IDF
- DE:Hesse
- DE:Saarland
- IT:Lazio
- IT:Emilia
- IT:Marche
- NL:East-Central
- PT:Northern
- PT:Lisbon
- UK:Northern
- UK:East Mid
- UK:Yorkshire/Humber
- SE:Stockholm
Impact on mortality and morbidity

<table>
<thead>
<tr>
<th></th>
<th>In-hospital mortality neonatal admissions)</th>
<th>Severe morbidity (survivors to discharge)</th>
<th>Mortality or morbidity neonatal admissions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All infants, N (%)</td>
<td>672/7336 (9.2)</td>
<td>669/6479 (10.3)</td>
<td>1341/7151 (18.8)</td>
</tr>
<tr>
<td>Receiving EB care, N (%)</td>
<td>241/4276 (5.6)</td>
<td>319/3927 (8.1)</td>
<td>561/4169 (13.5)</td>
</tr>
<tr>
<td>Not receiving EB care, N (%)</td>
<td>431/3060 (14.1)</td>
<td>350/2552 (13.7)</td>
<td>780/2982 (26.2)</td>
</tr>
</tbody>
</table>

Crude risk ratio, RR (95% CI) 0.42 (0.35 to 0.50) 0.56 (0.48 to 0.65) 0.51 (0.45 to 0.57)

Adjusted RR* (95% CI) 0.72 (0.60 to 0.87) 0.82 (0.71 to 0.94) 0.81 (0.72 to 0.90)

Propensity weighted RR (95% CI) 0.72 (0.60 to 0.87) 0.87 (0.75 to 1.02) 0.82 (0.73 to 0.92)

Adjusted for gestational age, sex, small for gestational age, multiple pregnancy, pregnancy complications, type of delivery, Apgar score, born on same day as maternal admission without in utero transfer, and region.
Potential reduction in mortality and morbidity if all infants received EB care

<table>
<thead>
<tr>
<th>Event</th>
<th>Observed Events</th>
<th>Reduction if all children received EB care</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths</td>
<td>672</td>
<td>120 (17.9)</td>
</tr>
<tr>
<td>Severe morbidity†</td>
<td>669</td>
<td>65 (9.7)</td>
</tr>
<tr>
<td>Death and/or severe morbidity</td>
<td>1341</td>
<td>151 (11.3)</td>
</tr>
</tbody>
</table>
Discussion

• Many of these factors associated with organization of care as well as non-implementation of EB practices within units

• Not all non-EB situations are « avoidable » - emergency deliveries outside of appropriate structures, not enough time for ANC administration...

• Use of minimum thresholds for evidence-based care to ensure acceptance. More stringent thresholds would decrease proportion of infants receiving EB care.
Summary

• All EB practices in less than 60% of infants admitted to neonatal care

• There are marked differences between regions concerning the use of EB care

• All 4 EB practices associated with an decreased risk of in-hospital mortality and morbidity

• The researchers calculated that, if full evidence based care had been provided to all infants, there would be an 18% reduction in all deaths = Better implementation of effective practices for the care of VPTI could lead to significant gains in mortality and morbidity
Research consortium

Coordination: INSERM U953, Paris
J Zeitlin (Project Coordinator), M Bonet (Project Manager)

- Studiecentrum voor Perinatale Epidemiologie, Brussels (P Van Reempts)
- Hvidovre Hospital, Hvidovre (O Pryds)
- Tartu University, Tartu (H Varendi)
- Philipps Universitaet Marburg, Marburg (RF Maier)
- Agenzia di Sanità Pubblica della Regione Lazio, Rome (D Dilallo)
- Ospedale Pediatrico Bambino Gesù, Rome (M Cuttini)
- Stichting Katholieke Universiteit, Nijmegen (L Kollée)
- Uniwersytet Medyczny im Karola Marcinkowskiego W Poznaniu, Poznan (J Gadzinowski)
- Faculdade de Medicina da Universidade do Porto, Porto (H Barros)
- Karolinska Institutet, Stockholm (M Norman)
- University of Leicester, Leicester (E Draper)

Funding

European Union's 7th Framework Programme

www.epiceproject.eu
SYMPOZJUM „PROFILAKTYKA, ROZPOZNANIE PRZYCZYN I LECZENIE NIEPŁODNOŚCI”

Data: 21 października 2016
Miejsce: Wielkopolski Urząd Wojewódzki w Poznaniu, Al. Niepodległości 16/18
Organizatorzy: Wielkopolski Urząd Wojewódzki w Poznaniu oraz Katedra i Klinika Neonatologii Uniwersytetu Medycznego w Poznaniu
Komitet Naukowy:
Przewodniczący: Prof. Janusz Gadzinowski
Członkowie: Prof. Bogdan Chazan, Prof. Jan Oleszczuk, Prof. Tomasz Ochędalski, Prof. Tadeusz Pietrucha, Prof. Marek Ruchała

Program Sympozjum:
08.00 – 09.00 Rejestracja uczestników
09.00 – 09.10 Otwarcie Sympozjum (Zbigniew Hoffmann – Wojewoda Wielkopolski)
09.10 – 09.15 Wprowadzenie (Prof. Janusz Gadzinowski)
09.15 – 09.45 Rodzicielstwo zdrowe od początku – profilaktyka niepłodności (Prof. Bogdan Chazan)
09.45 – 10.15 Endokrynologiczne przyczyny niepłodności (Prof. Marek Ruchała)
10.15 – 10.45 Przyczynowe leczenie niepłodności (Prof. Tomasz Ochędalski)
10.45 – 11.05 Przezpochwowe udarżnianie jajowodów w leczeniu niepłodności (Dr Krzysztof Pyra)
11.05 – 11.20 Dyskusja
11.20 – 12.00 Przerwa lunchowa
12.00 – 12.25 Metoda rozpoznawania płodności – istotny element promocji zdrowia prokreacyjnego (mgr Mirosława Szymaniak)
12.25 – 12.55 CREIGHTON MODEL Fertility Care System – klucz do rozpoznania stanu płodności kobiety (Dr Agnieszka Białecka)
12.55 – 13.40 Assessing the approaches and the outcomes of restorative procreative medicine and conventional reproductive medicine (Prof. Joseph Stanford)
13.40 – 14.10 Niepłodność jako problem wieloczynnikowej choroby przewlekłej. Diagnostyka i leczenie w oparciu o metody naprawcze w medycynie prokreacji (Dr Maciej Barczentewicz)
14.10 – 14.40 Dyskusja
14.40 – 14.45 Zakończenie Sympozjum

UDZIAŁ W SYMPOZJUM JEST BEZPŁATNY PO WCZEŚNIEJSZEJ REJESTRACJI

Szczegółowe informacje i rejestracja: www.sympozjum-nieplodnosc.pl