

Ethical conflicts in clinical trials in preterm labor

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Disclosures



- ❖ The views expressed are the authors' and do not represent the views or policies of the GFBR organization.
- ❖ Although this paper is based on a real case received at our local IRB, I am responsible for the discussion.
- ❖ I have not received financial support from pharmaceutical industry related to this topic (or to any other topic).



Outline



- ❖ The problems of prematurity.
- ❖ The use of tocolytic drugs to prevent premature labor.
- ❖ The research project.
- ❖ Discussion of the ethical issues related to clinical trials in preterm labor.

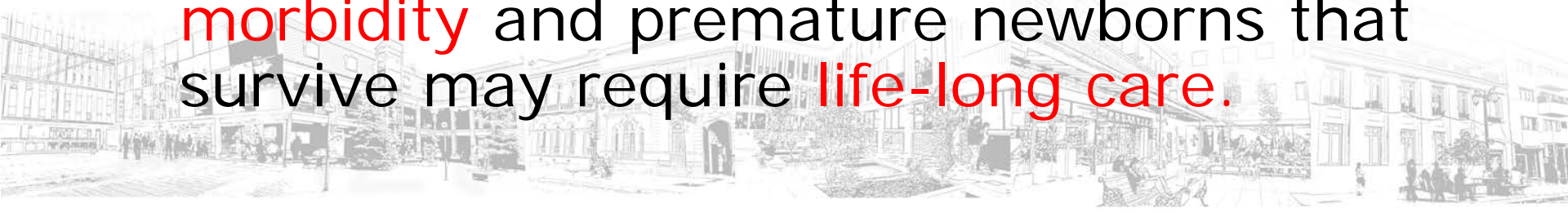


The problems of prematurity

- ❖ Preterm birth is defined as birth occurring between 20 - 36 wks G.A.



- ❖ Preterm complications are the leading cause of **death** among children under the age of 5.
- ❖ Preterm birth causes severe **neonatal morbidity** and premature newborns that survive may require **life-long care**.



Premature labor treatment



- ❖ Tocolytic drugs are used to prolong pregnancy for at least 48 h, providing a window for administration of antenatal corticosteroid or *in-utero* fetal transfer to an appropriate neonatal healthcare setting.
- ❖ At the time of submission of the research protocol, the most frequent drugs used in Chile were betamimetics:
 - ◆ They are effective in delaying birth at least 48 hours.
 - ◆ They produce maternal and fetal cardiovascular side effects, causing treatment discontinuations.



New tocolytic agent



- ❖ Atosiban is an oxytocin antagonist that inhibits preterm uterine contractions without significant cardiovascular, pulmonary or central nervous system side effects.
- ❖ At that time, data suggested that its use to delay labor would be as efficient as betamimetics, but with fewer side effects.



Research protocol



- ❖ **Aims:** to compare effectiveness and safety of the oxytocin receptor antagonist (**atosiban**) vs. a betamimetic (**salbutamol**) in the treatment of preterm labor.
- ❖ **Inclusion criteria:** maternal age between 16 and 44 years, singleton pregnancy, intact membranes, between 24 weeks' and 34 weeks' gestation; reported or documented uterine activity, and cervical dilation between 2 cm and 4 cm in an otherwise normal pregnancy.



Outcomes



- ❖ Primary: preterm birth (< 37 weeks);
- ❖ Secondary:
 - ◆ preterm birth within 48h of randomization,
 - ◆ at least 2 doses of corticosteroid administered prior to delivery,
 - ◆ preterm birth within 7 days of randomization.
- ❖ Both groups received standard obstetric and neonatal care, and there were no other interventions associated with the participation in the trial, except for strict data registration and two years non-invasive neonatal follow-up.



Ethical justification of the trial

- ❖ Inclusion of pregnant women in this type of research is justified:
 - ◆ The outcome of the trial is relevant to the health needs of pregnant women and their fetuses.
 - ◆ The study cannot be done in nonpregnant women.
 - ◆ The trial was supported by reliable evidence in animal studies and Phase I studies in non-pregnant women.



Ethical justification for local participation in the trial

- ❖ Premature labor is a condition prevalent in the country.
- ❖ Standard therapy with betamimetics has important health risks.
- ❖ The existence of a well-implemented neonatal intensive care unit.
- ❖ The new drug could be made available in the country and benefit the local population.



When to consent: Pain, fear, distress



When to consent?



- ❖ Local IRB suggested a pre-consent procedure and full information regarding the trial during normal pregnancy check-ups.
- ❖ This allowed enough time for women to consider enrollment and understand the maternal risks and potential benefits for the newborn of using the standard treatment or the new drug.



Is there a need of the father's consent?

- ❖ According to CFR 46.204 (e), if the research holds out the prospect of direct benefit solely to the fetus, then the consent of the **pregnant woman** and **the father** is obtained.
- ❖ According to Chilean research law, only the pregnant woman should give or deny the consent. However, father consent is always desirable.



Balance between the interests of the mother and the infant

- ❖ Prematurity poses health risk to the newborn.
- ❖ Tocolytic treatments pose health risks to the mother as well as to the fetus.
- ❖ IRB should establish **risk/benefit ratio** for both mother and the child during this type of trials.
- ❖ Important to determine actions if the initial treatment fails:
 - ◆ Rescue to standard drug?
- ❖ There is need of frequent reports from the external monitoring Committee.



Which are the obligations of the sponsor?

- ❖ The study design should choose a site that has the best standard of care.
- ❖ Those complications inherent to the condition (hospitalization, corticoid use, etc) should be paid by the social security but not by the research project.
- ❖ The sponsor should pay for the newborn follow-ups.
- ❖ The sponsor should have insurance to cover the expenses related to adverse effects.



Conclusions



- ❖ Inclusion of pregnant women as research subjects for acute medical conditions -such as threatened premature labor-, raises important ethical questions.
- ❖ Local IRB should consider not only the way that informed consent process is conducted, including the timing of consent, as well as how this research can be implemented safely within local facilities.



Thanks!



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