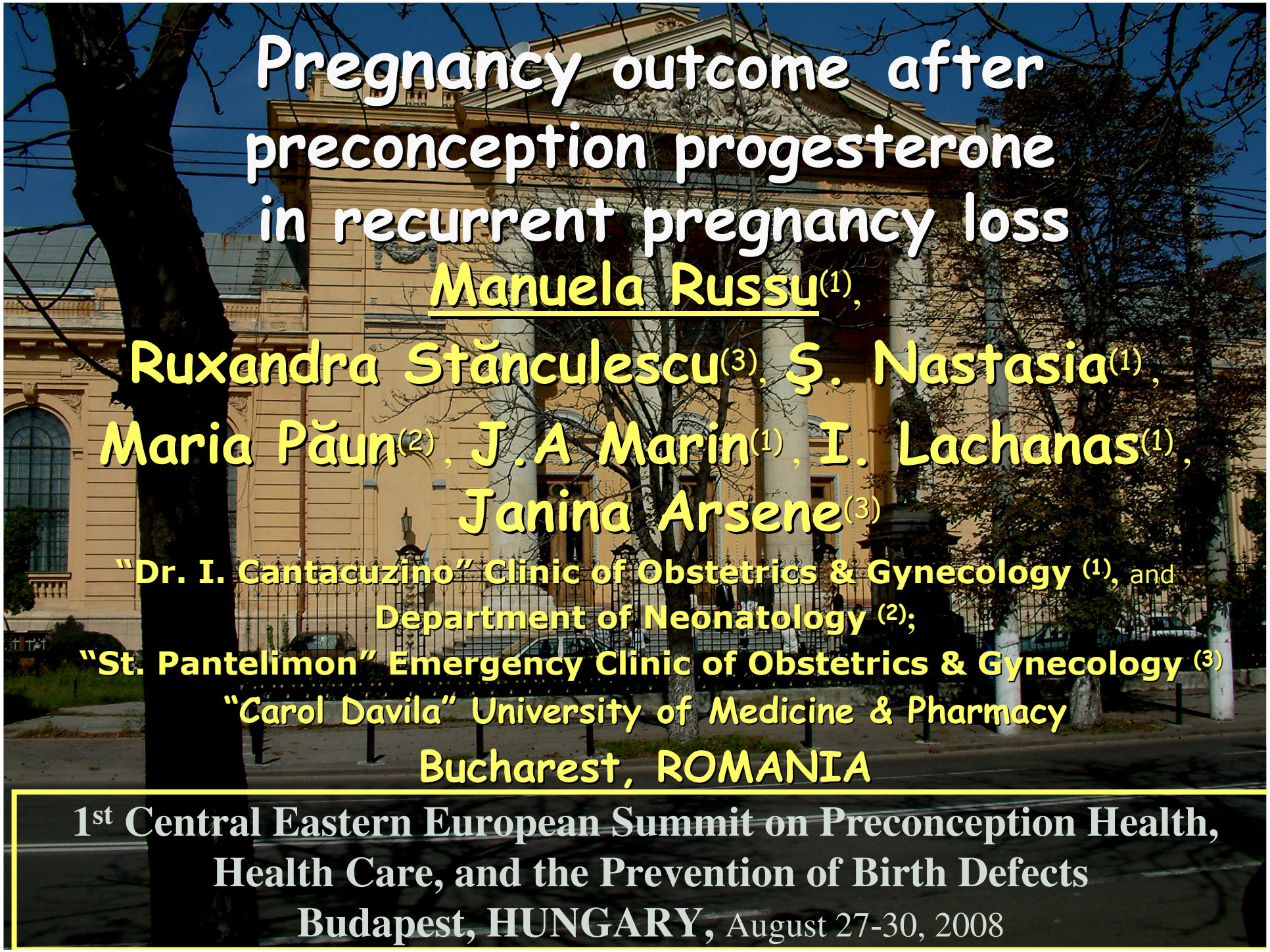

Pregnancy outcome after preconception progesterone in recurrent pregnancy loss

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Objectives

The assessment of
pregnancy outcomes after
preconception to 36 wks gestation
treatment with
1mg/d folic acid &
200mg/d vaginal micronized progesterone
in recurrent pregnancy loss

Material and methods (1)

Subjects: different by moment of 2 previous pregnancies loss: first trimester - group A and third trimester – early preterm birth with neonatal death or stillbirth, **- group B**

Patients are diagnosed and enrolled in two university clinics of obstetrics from "Carol Davila" University of Medicine and Pharmacy, Bucharest, if they accomplished inclusion & exclusion criteria

Inclusion Criteria: 2 pregnancy loss (first or third trimester)

Material and methods (2)

Exclusion Criteria:

- ✓ major uterine malformations,
- ✓ subtle ovulatory dysfunction, as that related to hyperprolactinemia,
- ✓ positivity for infections as: toxoplasmosis, listeriosis, CMV, syphilis,
- ✓ major chronic medical diseases (e.g.: insulin-requiring diabetes mellitus or pharmacologically treated hypertension), treatment with 10,000 or more units of unfractionated heparin per day, treatment with low-molecular-weight heparin at any dose or other diagnosed blood coagulation protein or platelet defects,
- ✓ previous pregnancies with chromosomal abnormalities as numeric abnormalities (aneuploidies) and structural anomalies (defects in the structure of 1 or more chromosomes),
- ✓ previous gestation over 42 weeks with fetal wastage

Material and methods (3)

- ✓ An ultrasonic examination was required between 12 and 20 weeks 6 days of gestation:
  - to confirm the duration of gestation,
  - to screen for major fetal abnormalities,
  - for the diagnosis of an ultrasonic large or restricted fetus, and
- ✓ repeated at 32 to 34 weeks to evaluate fetal growth

Material and methods (4)

Outcome measures

✓ **Primary**: birthweight, Apgar scores, congenital malformations, GA of preterm birth, composite neonatal morbidity rate, containing severe respiratory distress syndrome (RDS), bronchopulmonary dysplasia (BPD), intraventricular haemorrhage (IVH), necroziting enterocolitis (NEC), need of oxygen supplementation, & of mechanic ventilation, length of admission in NICU

✓ **Secondary**: time to conceive, moment of miscarriage, time until delivery: preterm birth before 32 and 37 weeks, maternal morbidity (gestational diabetes, gestational hypertension), maternal hospitalization for threatened of miscarriage/ preterm birth.

Statistical Analysis

Student test for comparison of each group of treated patients to controls (**P value**), by ANOVA method

P < 0.01 = statistical significant

Results (1)

- ✓ **Treated groups**: **32** (group A) + **6** (group B)

  6 months preconception treatment with **folic acid 1mg/d** & **vaginal micronized progesterone 200mg/d** (14 days/month, each night, from the 14th day of menstrual cycle), continued immediately after a positive pregnancy test (the 7th – 10th days of amenorrhea) and prolonged till the 36th week gestation

- ✓ **Control group**: **58**

  treated during pregnancy with non a specific antispastic muscle-relaxant mixture, when necessary.

Results (2)

Patients characteristics	Group A			Group B			Group C		
Number of patients	32 (22 + 10 miscarriages)			6 (6 + 0 miscarriage)			58 (41 + 17 miscarriages)		
Age (average) yrs	31.33 ± 4.54 p= 0.038			31.33 ± 4.54 p= 0.038			26.9 ± 4.77		
Gestation	gestation 2	gestation > 2		gestation 2	gestation > 2		gestation 2	gestation > 2	
	10 p= 0.056	22 p= 0.06		1 p= 0.00001	5 p= 0.39		9	32	
Parity	Primi gravidas	Para 2	Para >2	Primi gravidas	Para 2	Para > 2	Primi gravidas	Para 2	Para > 2
	12	9	1	3	2	1	5	4	7
Preconception Weight (average) (kg)	58.59 ± 9.27 p= 0.13			61.33 ± 12 p= 0.09			55.32 ± 7.39		
Height (cm) Average (limits)	160.8 (155-168)			160.5 (155-164)			158.8 (155-165)		
Weight gain (average) kg	16.77 ± 5.71 p= 0.001			14.33 ± 3.32 p= 0.24			11.95 ± 4.75		

Results (3)

Primary pregnancy outcomes

Infant outcome	Group A 22			Group B 6			Controls 41		
Fetal weight (g)	3100 ± 489.41 p= 0.001			3216 ± 537.27 P = 0.022			2506.1 ± 699.21		
Fetal weight (g)	< 1500g		< 2500g	< 1500g		<2500g	<1500		< 2500g
	0		1 P = 0.0001	0		0	4		16
Gestation Age at delivery	24-28 wks	29-34 wks	≥ 35 wks	24-28 wks	29-34 wks	≥ 35 wks	24-28 wks	29-34 wks	≥ 35 wks
	0	1 4.5%	21 96.5%	0	1 16.6%	5 83.4%	2 4.8%	16 39%	23 56%

Results (4)

Primary pregnancy outcomes

Infant outcome	Group A 22			Group B 6			Controls 41		
Apgar Score - 1 min - 5 min	8.45 ± 1.53 p= 0.40 8.77 ± 1.11 p= 0.21			4.83 ± 4.57 p= 0.14 4.83 ± 4.62 p= 0.13			8.05 ± 1.98 8.2 ± 1.99		
pH blood cord when Apgar < 7/5'	5 cases Apgar score < 7			2 cases Apgar score <7			15 cases Apgar score <7		
	< 7.20	7.21-7.24	>7.25	< 7.20	7.21-7.24	>7.25	< 7.20	7.21 - 7.24	>7.25
	3	0	2	2	0	0	4	5	6

Results (5)

Primary pregnancy outcomes

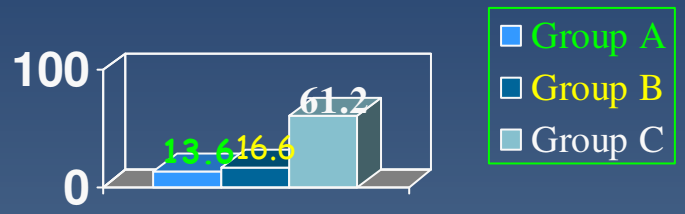
Infant outcome	Group A 22	Group B 6	Controls 41
Malformations	2 Hypospadias: group A, control		
	1 Criptorhydia: control		
	1 Hydrocele: control		
	1 Umbilical hernia: control		

Composite Neonatal Morbidity												
RDS			BPD			IVH			NEC			
A	B	C	A	B	C	A	B	C	A	B	C	
2	1	5	0	0	0	0	0	0	0	0	0	

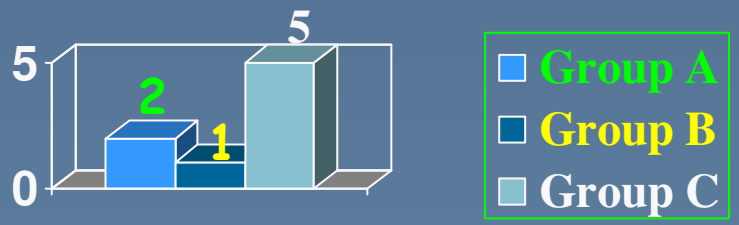
Results (6)

Primary pregnancy outcomes

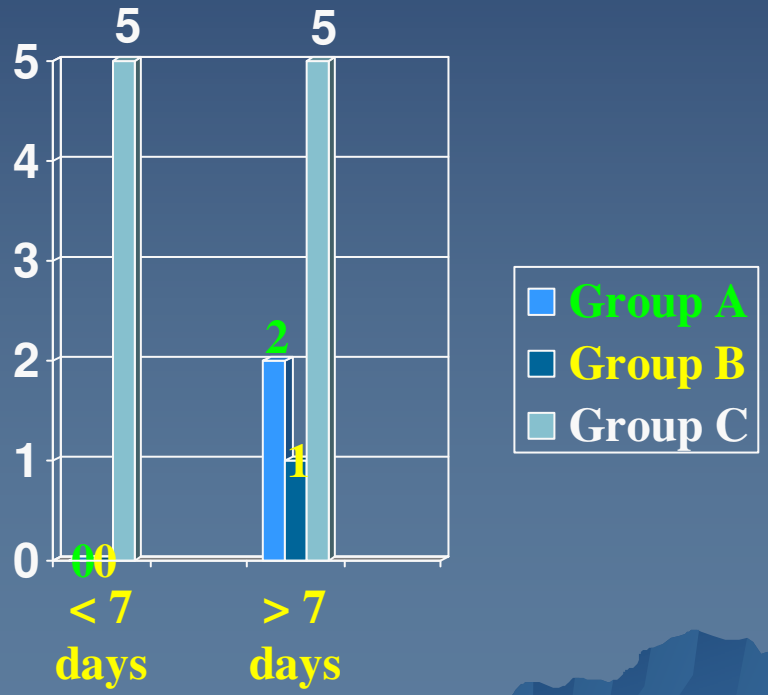
Need of oxygen supplementation (%)



Mechanical ventilation (no)



Lengh of admission in NICU (total no. of days)



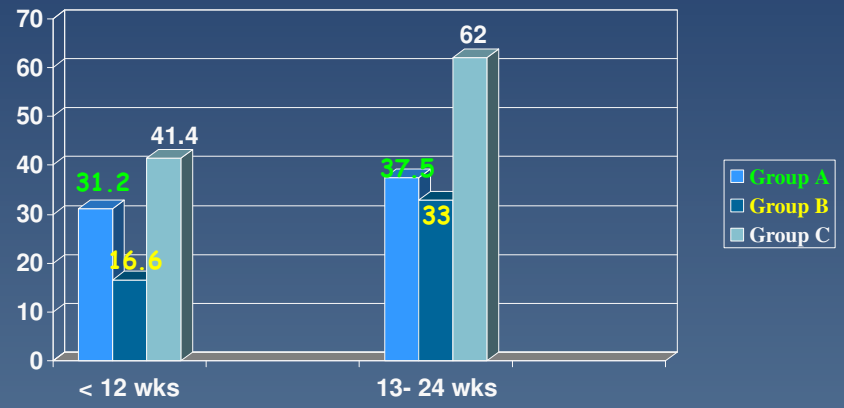
Results (7)

Secondary pregnancy outcomes	Group A 32 (22 + 10 miscarriages)		Group B 6 (6 + 0 miscarriage)		Group C 58 (41 + 17 miscarriages)	
Time to conceive	≤ 6 months	> 6 months	≤ 6 months	> 6 months	≤ 6 months	> 6 months
	27 86%	5 15.6%	5 83.3%	1 16.6%	36 60.7%	22 37.9%
Gestational age if miscarriage	< 12 wks	13-23 wks	< 12 wks	13-23 wks	< 12 wks	13-23 wks
	7 21.9%	3 9.3%	0	0	13 22.4%	4 7.2%
Stillbirth	0		1- 16.6%		2- 5%	
Fetal deaths before discharge	0		0		2 4.4%	

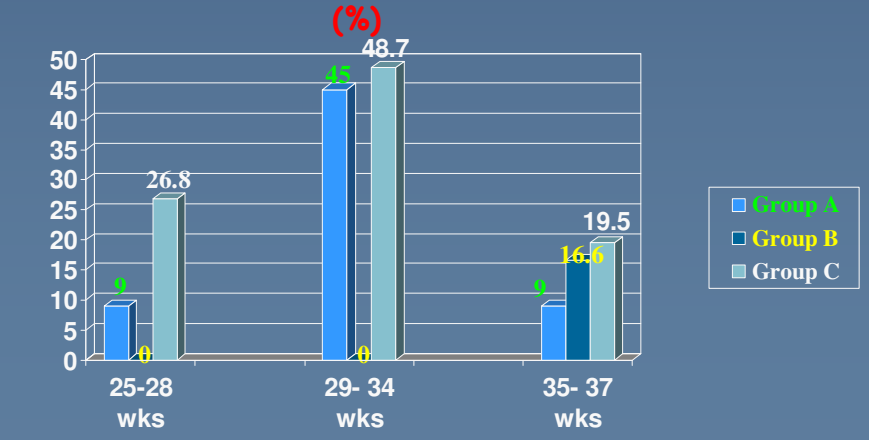
Results (8)

Secondary pregnancy outcomes

Hospitalization for threatened miscarriage (%)



Hospitalization for threatened preterm birth (%)



	Group A n= 22	Group B n= 6	Group C n= 41
Gestational hypertension	0	2 33%	3 19%
Gestational Diabetes	0	0	0

Discussions (1)

In the last 40- 50 years progestins and progesterone derivates have been administered during reproductive years for several reasons:

- ✓ luteal phase support when luteal phase defect or inadequate corpus luteum,
- ✓ spontaneous pregnancy achievement or IVF treatment,
- ✓ threatening miscarriage, recurrent miscarriage,
- ✓ prevention of preterm labor.

Discussions (2)

Only two formulations are considered safe:

- ✓ natural progesterone administered vaginally (as either a pessary or a cream),
- ✓ a synthetic caproate ester of naturally 17 alpha-hydroxyprogesterone*, given as a long-acting intramuscular injection.

*17 alpha-hydroxyprogesterone is produced by the placenta itself

Discussions (3)

- ✓ **micronized progesterone**: the only natural progesterone available in Romania, and
- ✓ **vaginal route of administration**: better bioavailability of Progesterone in the uterus (**10 fold higher to that of i.m. administration**) & **minimal systemic undesirable effects**

Cicinelli E, de Ziegler D, 1999

Tavaniotou A, Smitz J, Bourgain C, Devroey P, 2000

- ➢ because of a **first uterine pass effect**, explained by:
  - direct diffusion through tissue,
  - intracervical aspiration,
  - absorption into the venous or lymphatic circulatory systems, and
  - countercurrent vascular exchange with diffusion from utero- vaginal veins/lymph vessels to arteries

Discussions (4)

Devoto L, Vega M, Kohen P, et al, 2002

↓

✓ with aging the molecules (pro-inflammatory cytokines, reactive oxygen species, steroids and inducible nitric oxide synthethase) linked to apoptosis of corpus luteum

✓ are increasing, and

✓ are inducing a preferentially diminish of progesterone biosynthesis in mid and late luteal cells in culture

✓ In this study: maternal age in studied > controls

31.33 ± 4.54 vs 26.9 ± 4.77:

P = 0.038

Discussions (5)

- Preconception Progesterone supplementation by binding to the nuclear/membrane receptors:

- ✓ modulates the contractility of fallopian tubes & myometrium for gamete/embryo transportation throughout the uterotubal cavities and successful embryo implantation in spontaneous and/or assisted reproduction,

Goldenberg RL, Iams JD, et al, 1998

Ayoubi JM, Fanchin R, de Ziegler D, et al, 2001

Bulletti C, De Ziegler D, Cicinelli E, et al, 2004

Palagiano A, Bulletti C, de Ziegler D, Ciccinelli E, et al, 2004

Discussions (6)

Preconception Progesterone supplementation by binding to the nuclear or membrane receptors

✓ **maintains decidua viability** (Lan KKG, DeMets DL, 1983), together to estrogens **lower the vascular resistance in the uterine circulation**,

✓ **increases the rate of embryo implantation** by effect on endometrial stroma cells, **acting on different cytokine profiles** which are present as response of the female reproductive tract to the different paternal MHC histocompatibility antigens (the uterus = immunoprivileged site during pregnancy).

Discussions (7)

Progesterone enhances local production of Th2 and/or LIF cytokines which may contribute to the maintenance of pregnancy

- ✓ **Th1**- type cytokines are detrimental to pregnancy by stimulating NK- macrophage system that is involved in abortion, whereas
- ✓ **Th2-** type cytokines (and CD81 T cells) prevent abortions by suppressing of the NK-macrophage system, and inhibiting Th1 responses may allow allograft tolerance

Chaouat G, 1994

Discussions (8)

Progesterone enhances local production of Th2 and/or LIF cytokines which contribute to the maintenance of pregnancy

✓ **Leukemia inhibitory factor** - produced locally by deciduas, & **macrophage-stimulating factor** (M-CSF) are essential for embryo implantation, being associated with **Th-2**cells,

- **up-regulated** by **IL-4** and **progesterone** and
- **down-regulated** by **Th-1** type cytokines, and by **IL-12**, **IFN-γ**, and **IFN-α** (produced by Th-1)

Piccinni M, Beloni L, Livi C, et al, 1998

Piccinni M, Maggi E, Romagnani S, 2000

Discussions (9)

✓ The defective decidual production of LIF, M-CSF, Il -4, IL-10 (which is not found in peripheral-blood T-cells) and/or Th2 type cytokines may contribute to the development of unexplained recurrent abortions

Piccinni M, Scaletti C, Vultaggio A, et al, 2001

Szekeres-Bartho J, Barakonyi A, Miko E, et al, 2001

➢ Our study: Preconception progesterone supplementation during luteal phase was associated to a rate of immediate gestation (in less than 6 months) in 86% respectively 83.3% in groups A and B vs **60.7%** in controls; the supplementation was continued as soon as β HCG pregnancy test was positive (after 7 to 10 days from fertilization)

Discussions (10)

- ✓ Our protocol: sustaining corpus luteum, and both early & late pregnancy by vaginal micronized progesterone supplementation, in cases with high risk for recurrent pregnancy loss.
- ✓ Proctor A, Hurst BS, Marshburn PB, et al, 2006: have used either luteal protocol or first trimester protocol in IVF pregnancies, showing that in the luteal protocol the rate of miscarriage was higher than the first trimester protocol, but the rate of lifebirth was better (76.8% luteal protocol vs. 75.0% first trimester protocol; P = 0.80)

Discussions (11)

Progesterone supplementation was advocated for preterm prevention

Dodd JM, Flenady V, Cincotta R et al, for

Cochrane Database Syst Rev. 2006

Progestins/Progesterone derivates are suppressing **Thrombin- and Il-1{beta}-Induced Il -11**, which are related to preterm delivery, abruption placentae, and chorioamnionitis.

Cakmak H, Schatz F, Huang S-TJ, et al, 2005

IL-11 is a cytokine with pleiotropic biological effects, including induction of **Th-2** type, and inhibition of **Th-1** type cytokine responses, paradoxically, it enhances the synthesis of prostaglandins, which induce labor.

Discussions (12)

Natural Progesterone/ 17 alpha-hydroxyprogesterone are administered for miscarriage & preterm birth prevention at different pregnancy's ages:

- ✓ from **16-20 wks to 36 wks**: Meis PJ, Klebanoff M, Thom E, et al (2003) for National Institute for Child Health and Human Development: reduced the rate of delivery before 32 wks from **18.6%** to **11.4%** (P: 0.0180), and before 35 wks from **30.6%** to **20.6 %** (P: 0.0165)
- ✓ **24-34 wks**: da Fonseca EB, Bittar RE, Carvalho MH, Zugaib M, 2003: reduced the rate of delivery before 34 wks from 34% to 19%

Our protocol: **Preconception – 36 wks**: the rate of delivery after 35 wks increased from 56% to 96.5%

Conclusion (1)

Vaginal micronized progesterone & Folic acid preconception, in early and late pregnancy in recurrent pregnancy loss are followed by:

- ✓ A significant reduction of preterm birth before 34 wks (13.6% treated vs 36.6%controls),
- ✓ A reduction of miscarriages (23.7% treated vs 27,7% controls),
- ✓ An increase of birthweight (P=.001, group A; P=.022 group B), less cases with reduced blood cord pH (P=.0001-groupB) when Apgar score <7/5 minutes,

Conclusion (2)

Folic acid & vaginal micronized progesterone preconception, in early and late pregnancy in recurrent pregnancy loss are followed by:

- ✓ Less number of cases who need oxygen supplementation (10.5% vs 61.2%), and mechanical ventilation (7.6% studied vs 12.1% control)
- ✓ Less number of days of admission in the NICU (> 7 days: 7.6% studied vs 12.1% control)

Conclusion (3)

Vaginal micronized progesterone & Folic acid preconception, in early and late pregnancy in recurrent pregnancy loss are followed by:

- ✓ less neonatal morbidity (only RDS: 10.3% treated vs 12.2%controls),
- ✓ a nonsignifiant difference in perinatal mortality;
- ✓ 2 cases with hypospadias (group A, controls), more other abnormalities in controls.

Conclusion (4)

Vaginal micronized progesterone & Folic acid preconception, in early and late pregnancy in recurrent pregnancy loss are followed by:

- ✓ Less time to conceive (< 6 months: 81.3 % studied vs 60.7% control)
- ✓ Lower incidence of gestational hypertension in treated (5.2%) vs controls (19%), no gestational diabetes,
- ✓ Less hospitalization for miscarriage threaten (28.6% treated vs 48.8% control),
- ✓ Less hospitalization for preterm birth threaten (35.1% studied vs 43.8% control)


Thank you
VĂ MULȚUMESC
Kőszőnm a szives figyelműket