

***FORTUNATO VESCE***

**PREVENZIONE DELLA 'PREGNANCY LOSS'  
CON GLICOCORTICOIDI A BASSE DOSI:  
UNA SCELTA BASATA SULL'EVIDENZA**

***FERRARA, 24 MAGGIO 2014***

**DEPOPROVERA E DUVADILAN !**

GRAVIDANZA FISIOLOGICA  
PERFUSIONE UTERO-PLACENTARE  
QUIESCENZA MIOMETRIALE

**'PREGNANCY LOSS'**  
COAGULAZIONE  
CONTRAZIONE

**IOPERFUSIONE =  
ABORTO INTERNO, MALFORMAZIONE,  
IUGR, GESTOSI**

**CONTRAZIONE =  
ESPULSIONE DEL PRODOTTO DEL  
CONCEPIMENTO**

**ABORTO = PARTO PREMATURO**

**ABORTIVITÀ**

**SPORADICA = RECIDIVANTE**

**CITOCHINE**

**PROSTAGLANDINE**

**IPOPERFUSIONE**

**CONTRAZIONE**

## **ABORTO EUPLOIDE = ABORTO ANEUPLOIDE**

### **CYTOKINE IMBALANCE IN PREGNANCIES WITH FETAL CHROMOSOMAL ABNORMALITIES**

**(VESCE F., ET AL HUM REPROD 2007;(3)803-8)**

**RIDOTTA ESPRESSIONE DI IL8 (CHE STIMOLA LA PROSTACICLINA) E AUMENTO DI IL6 (CHE STIMOLA PG)**

### **PLASMINOGEN ACTIVATOR SYSTEM IN SERUM AND AMNIOTIC FLUID OF EUPLOID AND ANEUPLOID PREGNANCIES**

**( VESCE F. ET AL., OBSTET GYNECOL2001;(3):404-8)**

(chromosomal abnormalities had significantly higher serum levels of urokinase plasminogen activator and its complexed form with its type-1 inhibitor compared with euploid pregnancies)

### **RAISED LEVEL OF AMNIOTIC ENDOTHELIN IN PREGNANCIES WITH FETAL ANEUPLOIDY**

**( VESCE F. ET AL., FETAL DIAGN THER 1996;11(2):94-8)**

**Trophoblast cells induce a tolerogenic profile in dendritic cells.**

Hum Reprod. 2012 Sep;27(9):2598-606.

The interaction of DCs with trophoblast cells promotes the differentiation of DCs into cells with a predominantly tolerogenic profile that could contribute to a tolerogenic microenvironment at the maternal-fetal interface

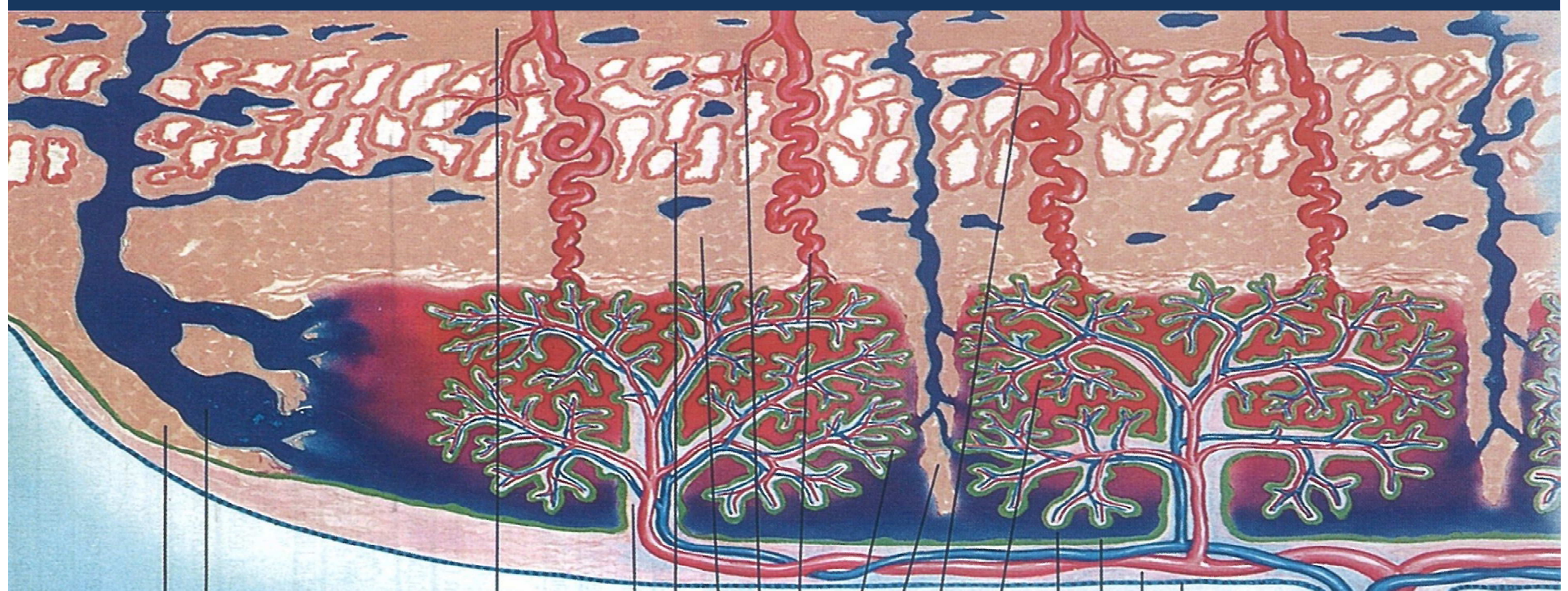
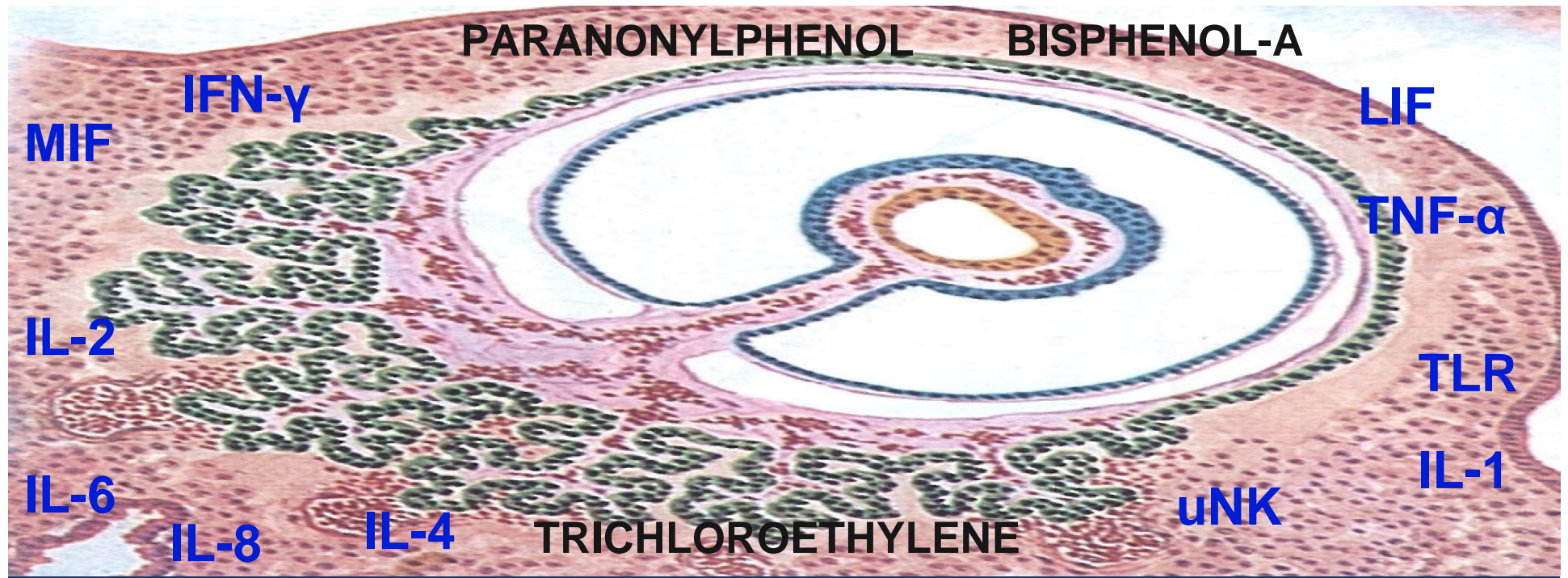
# GRAVIDANZA FISIOLOGICA MEDIATORI

- INTERFACCIA MATERNO-FETALE
  - INTERFERONE
  - INTERLEUKINE
- LEUKEMIA INHIBITORY FACTOR
  - TUMOR NECROSIS FACTOR
- TRANSFORMING GROWTH FACTORS
- COLONY STUMULATING FACTORS
- VASCULAR ENDOTHELIAL GROWTH FACTORS
- MACROPHAGE MIGRATION INHIBITORY FACTOR (MIF)
  - TOLL-LIKE RECEPTORS

■ [Curr Pharm Des.](#) 2010;16(32):3616-37.

■ **Use of glucocorticoids in pregnancy.**

■ [Lunghi L<sup>1</sup>](#), [Pavan B](#), [Biondi C](#), [Paolillo R](#), [Valerio A](#), [Vesce F](#), [Patella A](#).



## MIF TROFOBLASTICO

- >  $\text{TNF}\alpha$ ,  $\text{IFN}\gamma$ ,  $\text{IL-1}\beta$ ,  $\text{IL-2}$ ,  $\text{IL-6}$ ,  $\text{IL-8}$
- > PRODOTTI DELL'AC. ARACHIDONICO
  - > NO
  - < TOSSICITÀ NK DECIDUALI

# IL-1

**TRFOBLASTO E DECIDUA**

**SINCIZIO > HCG**

**> IL-6, IL-8, LIF, TNF- $\alpha$ , PG-2,**

**> IL-1 $\beta$  TUBARICA = GRAVIDANZA  
ECTOPICA**

# TOLL-LIKE RECEPTORS

## RECETTORI PER MOLECOLE ASSOCIATE AI PATOGENI

### TROFOBLASTO STROMA DECIDUALE

- [Eur J Obstet Gynecol Reprod Biol.](#) 2012 Dec;165(2):326-30. doi: 10.1016/j.ejogrb.2012.08.005. Epub 2012 Sep 1.
- **Increased expression of Toll-like receptor 3 in decidual natural killer cells of patients with unexplained recurrent spontaneous miscarriage.**

# ENDOCRINE DISRUPTORS

**PARA-NONYLPHENOL (p-NP)**

**BISPHENOL-A**

**TRICHLOROETHYLENE**

**INFLUENZANO CITOCHINE,  
DIFFERENZIAZIONE, APOPTOSI**

# ENDOCRINE DISRUPTORS

- [Reprod Sci.](#) 2012 Feb;19(2):181-9.

**Endocrine disruptors, polychlorinated biphenyls-induced gC1qR-dependent apoptosis in human trophoblast cell line HTR-8/SVneo.**

- [Immunotoxicol.](#) 2007 Apr;4(2):129-41

**Trichloroethylene alters central and peripheral immune function in autoimmune-prone MRL(+/-) mice following continuous developmental and early life exposure.**

# ENDOCRINE DISRUPTORS-ABORTION

- Hum Reprod. 2005 Aug;20(8):2325-9.
  - Sugiura-Ogasawara M, et al.
- Exposure to bisphenol A is associated with recurrent miscarriage.
  
- Zhonghua Yu Fang Yi Xue Za Zhi. 2011 Apr;45(4):344-9.
- [A correlative study on Bisphenol A and recurrent spontaneous abortion].

# POLIMORFISMI GENETICI DI TIPO INFIAMMATORIO

Holst D, Garnier Y. Eur J Obstet Gynecol Reprod Biol. 2008 Nov;141(1):3-9.

Preterm birth and inflammation-The role of genetic polymorphisms.  
polymorphisms that increase the magnitude or the duration of the inflammatory response were associated with an increased risk of preterm birth. In contrast polymorphisms that decrease the inflammatory response were associated with a lower risk of preterm birth.

Engel SA, et al Epidemiology. 2005 Jul;16(4):469-77.

Risk of spontaneous preterm birth is associated with common proinflammatory cytokine polymorphisms.

Common genetic variants in proinflammatory cytokine genes could influence the risk for spontaneous preterm birth.

Annells MF, et al BMC Pregnancy Childbirth. 2005 Feb 21;5(1):4.

Polymorphisms in immunoregulatory genes and the risk of histologic chorioamnionitis in Caucasoid women: a case control study.

Polymorphisms in immunoregulatory genes IL10, MBL2, TNFRSF6 and TGFB1 may influence susceptibility to chorioamnionitis.

**GLICOCORTICOIDI: DOSIS FACIT VENENUM**

**CON QUALE MECCANISMO ?**

**A QUALE CONCENTRAZIONE ???**

**A quale livello ??????????????**

# Blastocyst attachment

Embryo implantation requires a molecular dialogue initiated during blastocyst attachment by cell surface signalling molecules on the trophoblast and endometrium, such as the **integrins and fibronectin**

(Burrows et al., 1996)

Glucocorticoids can suppress the expression of trophoblast integrins, hence modulating these initial trophoblast-decidua interactions.

(Ryu et al., 1999)

## CONNESSINE TROFOBLASTICHE

- Betamethasone, progesterone and RU-486 (mifepristone) exert similar effects on connexin expression in trophoblast-derived HTR-8/SVneo cells.
- Cervellati F, Pavan B, Lunghi L, Manni E, Fabbri E, Mascoli C, Biondi C, Patella A, **Vesce F.**
- **Reprod Fertil Dev. 2011;23(2):319-28. doi: 10.1071/RD10077.**

# Cellular actions of glucocorticoids

**The chronic actions of glucocorticoid are typically mediated via intracellular glucocorticoid receptors (GR)**

(Funder, 1997; Kino and Chrousos, 2004; Lu et al., 2006).

**GR are expressed at high levels in:**

**decidua, chorion, amnion, stromal fibroblasts, vascular smooth muscle cells and endothelial cells from term human placental villi, with moderate expression in term cytotrophoblasts and negligible expression in the term syncytiotrophoblast**

(Kossmann et al., 1982; Lee et al., 2005; Chan et al., 2007; Yang et al., 2007).

# The inflammatory cascade and embryo implantation

**Successful implantation requires a coordinated sequence of inflammatory events, with key roles for pro-inflammatory cytokines:**

- **interleukin (IL)-1**
- **tumour necrosis factor (TNF)- $\alpha$**
- **prostaglandins**

(Chard, 1995; Sharkey, 1998; Kelly et al., 2001; Staun-Ram and Shalev, 2005; Achache and Revel, 2006; Makrigiannakis et al., 2006).

**Glucocorticoids are known to exert several anti-inflammatory actions which could impair the cytokine-prostaglandin signalling cascade required for implantation**

DOBBIAMO DUNQUE CONCLUDERE CHE I  
GLICOCORTICOIDI FACCIANO MALE?

CHE OSTACOLINO I FISIOLGICI PROCESSI  
GESTAZIONALI?

CERTAMENTE NO !

PARACELSO :  
DOSIS FACIT VENENUM

# Glucocorticoid interactions with cytokines

In first trimester human cytotrophoblast cells, cortisol can suppress the synthesis of the pro-inflammatory IL-1b  
(Librach et al., 1994).

in term human placenta and decidua, physiological concentrations of cortisol and several synthetic glucocorticoids inhibit both basal and bacterial lipopolysaccharide (LPS)-stimulated output of the pro-inflammatory cytokines, TNF-a, IL-6 and IL-8 by over 70% **without affecting expression of the anti-inflammatory cytokine IL-10 .**

(Rosen et al., 1998; Ma et al., 2004, 2006; Xu et al., 2005)

Michael AE and Papageorghiou AT, 2008

Glucocorticoids improve:

- **pregnancy rate** in women undergoing in vitro fertilization-embryo transfer (IVF-ET)  
(Boomsma et al., 2007)
- **pregnancy outcomes** in women with a history of recurrent miscarriage (Ogasawara and Aoki, 2000; Quenby et al., 2003, 2005)

NATURAL KILLER !

## USO E DOSI

betametasone 0,6 mg = prednisone 5 mg

WELLS, 1953: IPEREMESI:cortisone 25-75 mg/day fino a 64 giorni

BLOCCO ATRIO-VENTRICOLARE FETALE = DESAMETASONE

IPIERPLASIA SURRENALICA = DESAMETASONE DALLA 10° SETT

MALFORMAZIONE ADENOMATOIDE CISTICA FETALE = BETAMETASONE

PIASTRINOPENIA ALLOIMMUNE=PREDNISONE 10 mg DA 23 SETT

ABORTO RICORRENTE: QUEENBY PREDNISOLONE 5mg-poi 20mg

ATC-ANTIFOSFOLIPIDI=0'5-08mg PREDNISOLONE/kg

PROCREAZIONE ASSISTITA=DESAMETASONE BASSE DOSI

RDS= BETAMETASONE

ENTEROCOLITE NECROTIZZANTE = BETAMETASONE

ENCEFALOPATIA EMORRAGIA ITV = BETAMETASONE

## Relative potencies of corticosteroids used in treatment

(R. K. Sidhu. Corticosteroids in pregnancy.

In : Drugs and pregnancy,166-79. Edited by D. F. Hawkins, Churchill Livingstone 1987)

Compound	Relative anti-inflammatory potency	Relative sodium-retaining potency
Dexamethasone	25.0	0
Betamethasone	25.0	0
Paramethasone	10.0	0
Fludrocortisone	10.0	125.0
Triamcinolone	5.0	0
Methylprednisolone	5.0	0.5
Prednisolone	4.0	0.8
Hydrocortisone	1.0	1.0
Cortisone	0.8	0.8

# **PASSAGGIO TRANSPLACENTARE**

**11- $\beta$ - IDROSSI-STEROIDO-DEIDROGENASI-1:  
CORTISOLO E CORTICOSTERONE TRASFORMATI  
IN CORTISONE (INATTIVO)**

**OLTRE ALLA POTENZA ANTI-INFIAMMATORIA  
CONSIDERARE L'INATTIVAZIONE!**

**RIDOTTA DAL PROGESTERONE !**

**STIMOLATA DAI GLICOCORTICOIDI !!  
E DALL' IL-1 $\beta$  !!**

## PENSANDO ALL'EFFICACIA E ALL'INATTIVAZIONE

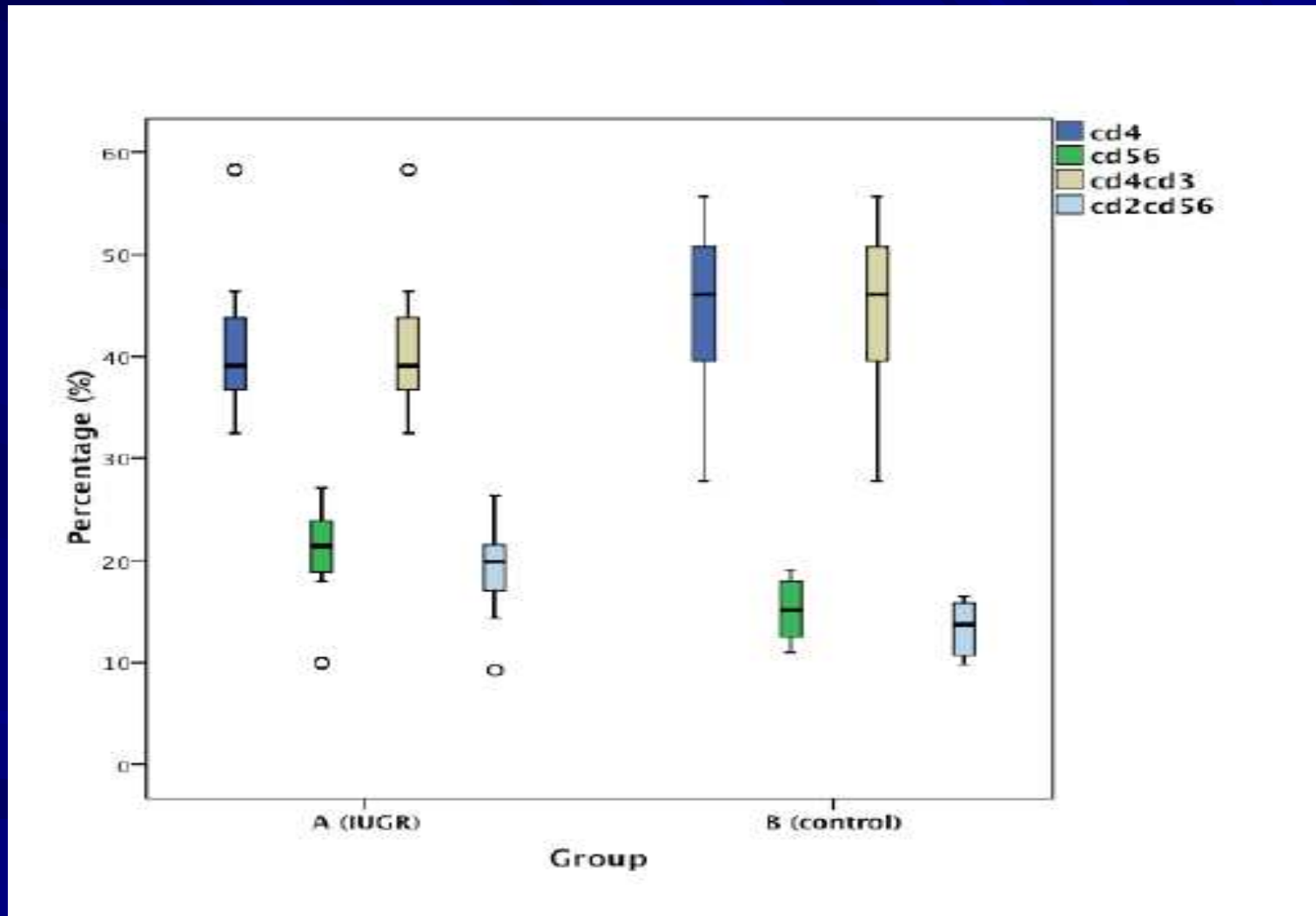
IL PREDNISOLONE HA UNA POTENZA BIOLOGICA CIRCA 5 VOLTE INFERIORE RISPETTO AL BETAMETASONE E AL DESAMETASONE E VIENE QUASI COMPLETAMENTE INATTIVATO A LIVELLO UTERO-PLACENTARE: PER QUESTO DEVE ESSERE SOMMINISTRATO AD ALTE DOSI

# pNK

■ > IUGR

(VESCE F, et al. The role of glucocorticoids in pregnancy: four decades experience with use of betamethasone in the prevention of pregnancy loss. In 'Glucocorticoids – new recognition of our familial friends', chapter 16, pag. 407-48, editor XIAOXIAO QIAN, INTECH, November 2012)

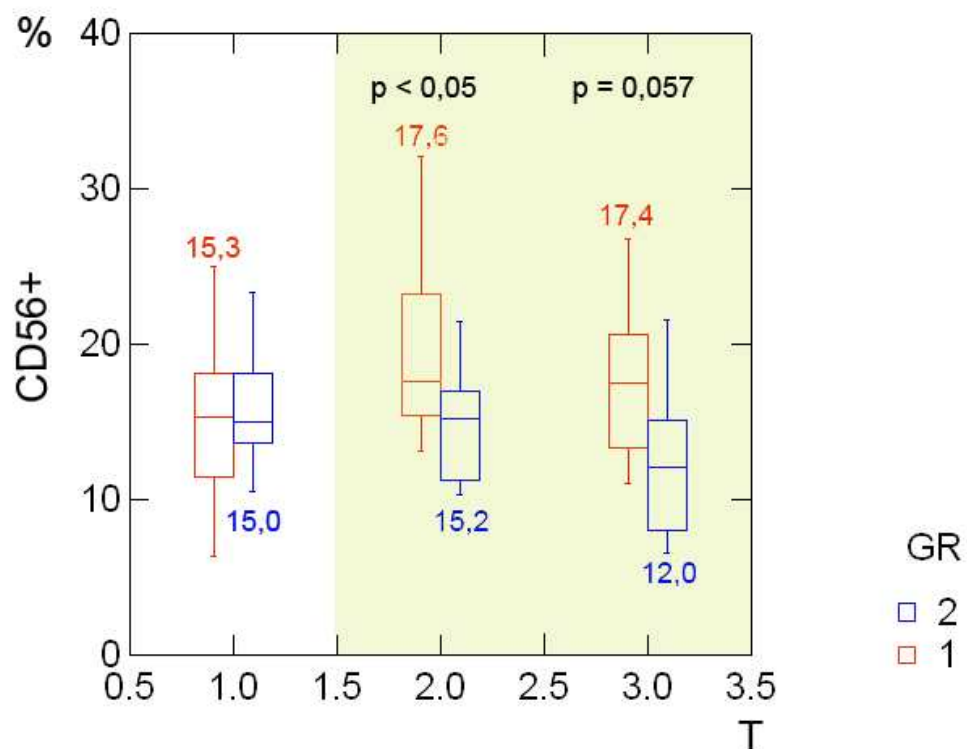
## Graphical representation of the different lymphocyte percentage between IUGR and control groups.





## NELL'ARCO DELLA GRAVIDANZA CON STORIA DI RSA IN TERAPIA CON BETAMETASONE

↓ leucociti, ↓ linfociti, ↓ percentuale cellule NK



### Casi vs controlli

In t1 no differenze

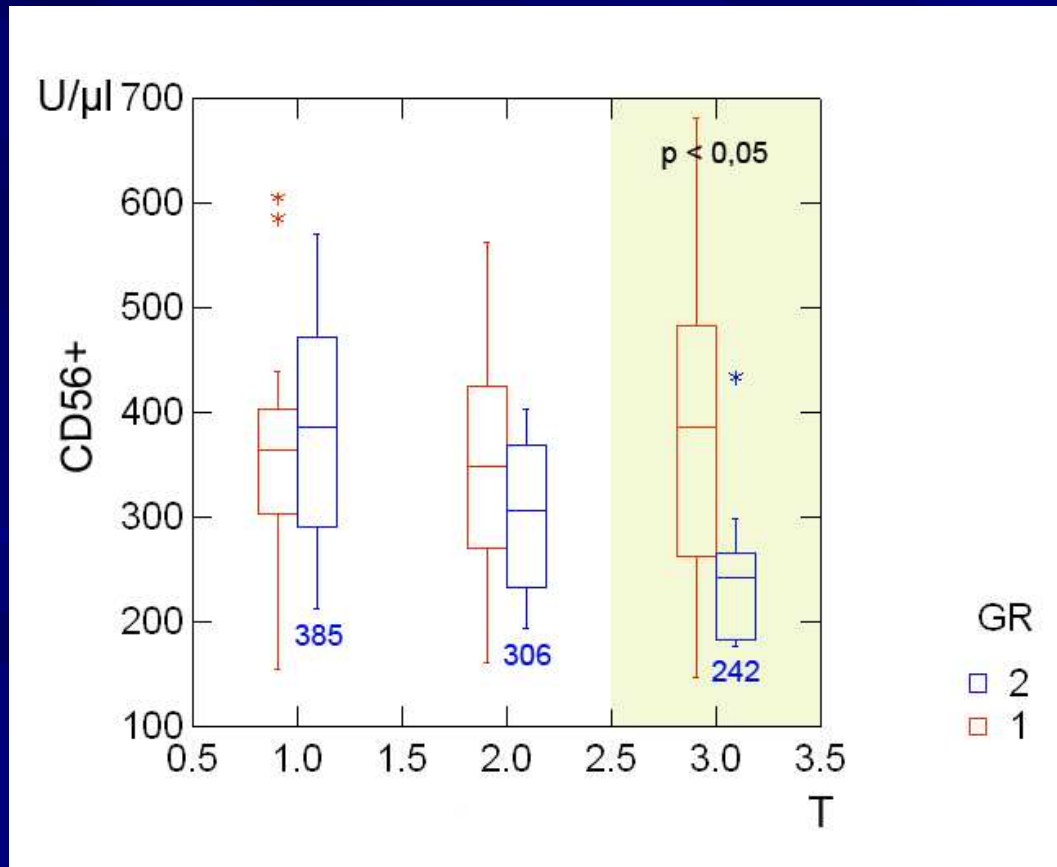
In t2 percentuale < rispetto  
ai controlli (p<0,05)

In t3 percentuale < rispetto  
ai controlli (p=0,057)



## GRAVIDANZE CON STORIA DI RSA IN TERAPIA CON BETAMETASONE

↓ valore assoluto cellule NK



### Casi vs controlli

In t1 e t2 no differenze

In t3 percentuale < rispetto ai controlli (p<0,05)

# GLUCOCORTICOIDI E PESO FETALE

80 PZ RSA , BETAMETASONE 0,5mg = 2843 g  
60 CONTROLLI = 3262 g

26 pz (preeclampsia, parto prematuro, diabete gestazionale, ipotiroidismo, asma bronchiale)

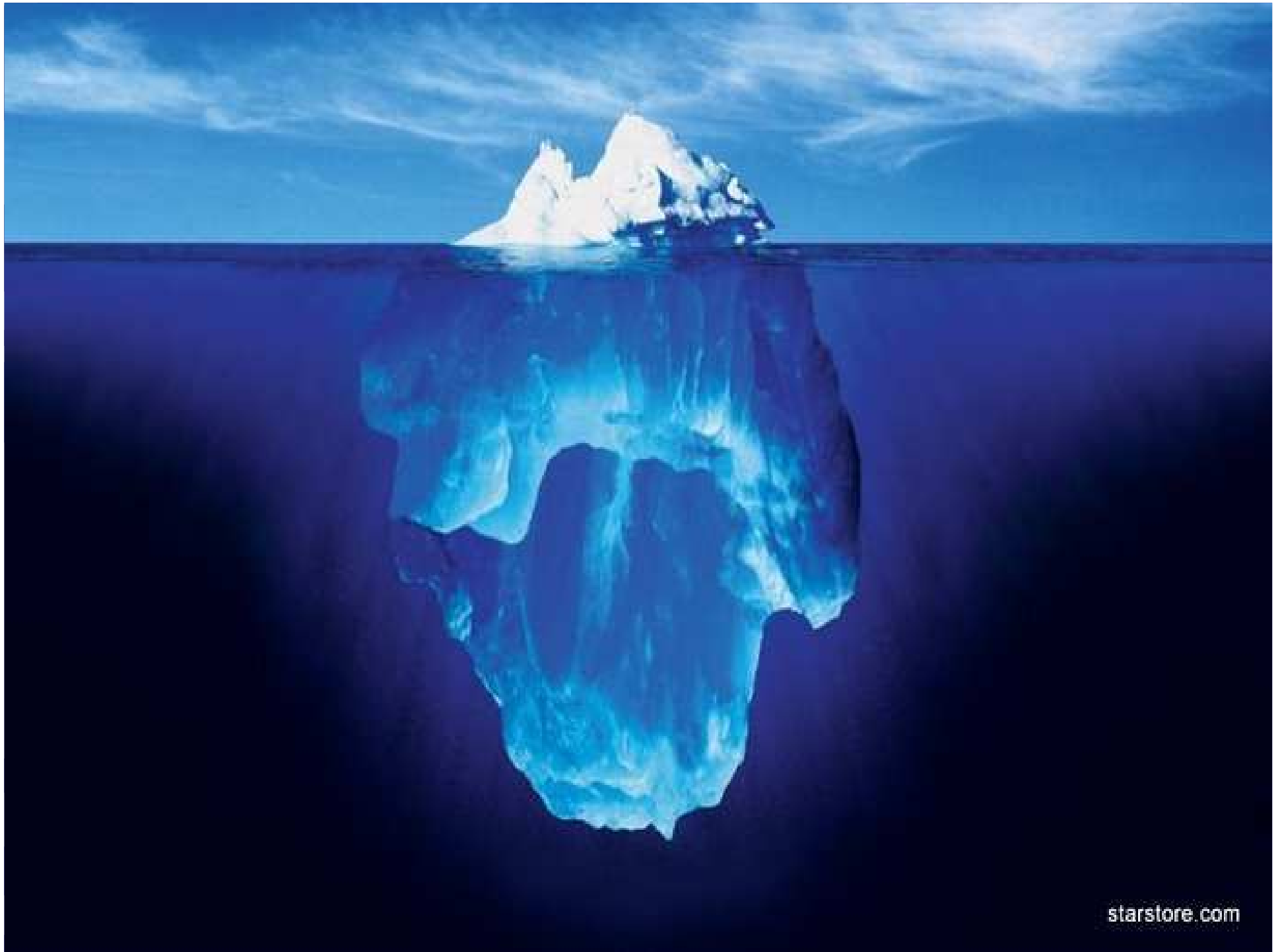
RSA TRATTATE = 3144 g  
CONTROLLI = 3262 g (N.S.)

**UN TERZO DEI CASI = PESO > 50%**

VESCE F, et al. The role of glucocorticoids in pregnancy : four decades experience with use of betamethasone in the prevention of pregnancy loss. In 'Glucocorticoids – new recognition of our familial friends', chapter 16, pag. 407-48, November 2012

*Low dose of Betamethasone throughout the whole course of pregnancy and fetal growth: a clinical study.*

Vesce F, Giugliano E, Cagnazzo E, Mossuto E, Marci R.  
Eur Rev Med Pharmacol Sci. 2014 Feb;18(4):593-8.



## CONCLUSIONI

- **GLI INSUCCESSI DELLA GRAVIDANZA SONO DOVUTI ALLO SBILANCIAMENTO DEI MEDIATORI FISIOLGICI (CITOCHINE E PROSTANOIDI).**
- **I GLICOCORTICOIDI SONO IN GRADO DI RIPRISTINARE L'EQUILIBRIO**
- **LA SOMMINISTRAZIONE DI BASSE DOSI DI BETAMETASONE PER TUTTA LA DURATA DELLA GRAVIDANZA RISULTA ALTAMENTE EFFICACE NELLA PREVENZIONE DELL'ABORTO RECIDIVANTE COME DI QUELLO SPORADICO.**
- **GLI EFFETTI NEGATIVI DEI GLICOCORTICOIDI PAVENTATI IN LETTERATURA SONO DA ATTRIBUIRE PIUTTOSTO ALL'USO DI DOSI IMPROPRIE, E NON SONO EMERSE NEL CORSO DELLA NOSTRA QUARANTENNALE ESPERIENZA**