
Department of Obstetrics
&
Gynaecology
Prenatal & Preimplantation
Genetic Diagnosis
Fetal Therapy
Cagliari
Ospedale Regionale Microcitemie
WHO
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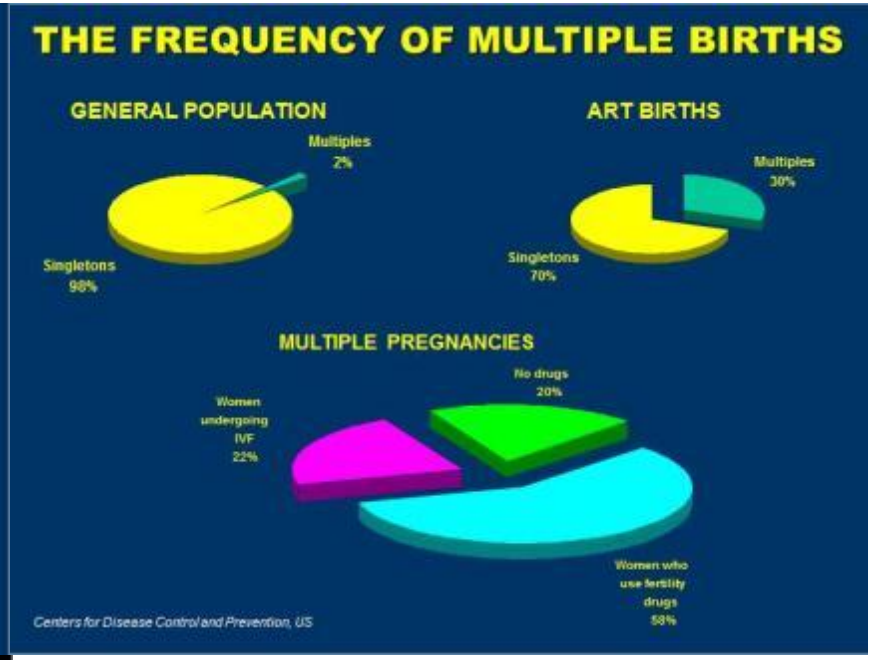
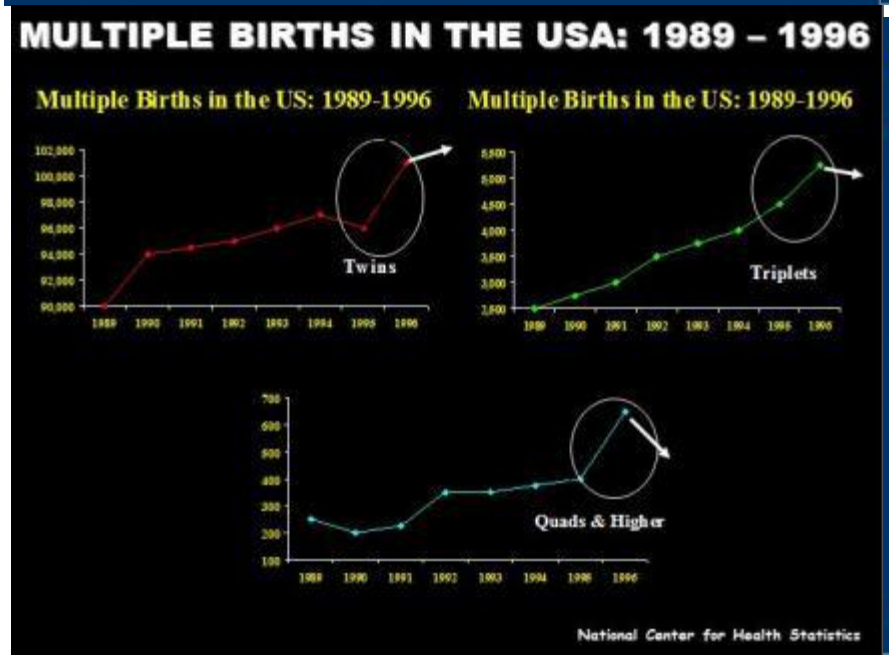
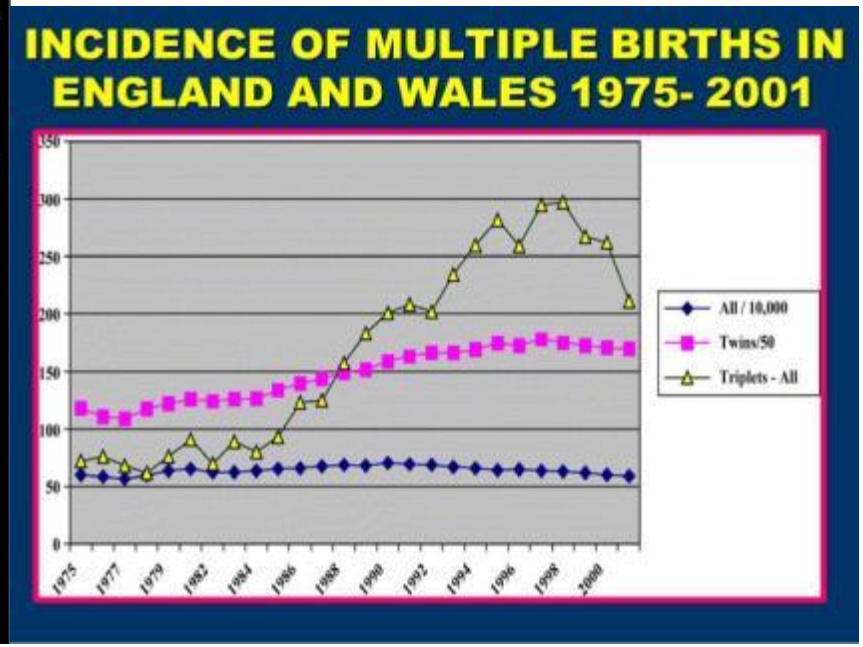
of
Hereditary Diseases
MULTIFETAL EMBRYO REDUCTION
IN VERY HIGH MULTIPLES
Giovanni Monni
Ho Chi Minh City, March, 2011


THE FREQUENCY OF MULTIPLE BIRTHS
GENERAL POPULATION
Multiples
2%
Singletons
98%
ART BIRTHS
Multiples
30%
Singletons
70%
MULTIPLE PREGNANCIES
No drugs
20%
Women
undergoing
IVF
22%
Women who
use fertility
drugs
58%
Centers for Disease Control and Prevention, US


MULTIPLE BIRTHS IN THE USA: 1989 – 1996
Multiple Births in the US: 1989-1996
Twins
Multiple Births in the US: 1989-1996
Triplets
Quads & Higher
National Center for Health Statistics


INCIDENCE OF MULTIPLE BIRTHS IN
ENGLAND AND WALES 1975- 2001
All / 10,000
Twins/50
Triplets - All

MULTIPLE DELIVERY IN EU and ITALY 2004- ESHRE report

	Twins	Triplets/+
IVF and ART		
All ESHRE	21.7 %	1%
Italy	21.3%	2%
Intrauterine insemination (husband semen)		
All ESHRE	10.4%	0.3%
Italy	13.2%	2.9%

Andersen, Hum Reprod 2008

PREVENTION OF ART MULTIPLE GESTATIONS

- Careful monitoring during treatments with fertility drugs
- Limit the number of embryos trasferred during in vitro fertilization. Transfer of multiple embryos may not improve delivery rates, but clearly increases the risk of a multiple pregnancy
- Using the technique known as blastocyst transfer, that enable to better select the embryos.

HIGH ORDER MULTIPLES (HOM) an heterogeneous entity.....

TRIPLETS

QUADRUPLETS and GRAND ORDER MULTIPLES

MONOCHORIONICITY

TRICHORIONIC TRIAMNIOTIC TRIPLETS

9-PLETS

TRICHORIONIC TRIAMNIOTIC QUADRUPLETS (conjoined twin)

DICHORIONIC TRIAMNIOTIC TRIPLETS

HIGH ORDER MULTIPLES (HOM) EFFECT

- Increased maternal risk
- Increased fetal/neonatal mortality
- Increased neonatal morbidity
- Increased financial and social costs

MATERNAL RISKS OF HIGH ORDER MULTIPLES

- Treatment of preterm labor
- Prolonged hospitalization with secondary increased risk of
  - Venous tromboembolism
  - Muscle atrophy
  - Osteopenia
  - Psychological distress
- Pregnancy induced hypertension
  - Preeclampsia, Severe preeclampsia (24%)
  - HELLP syndrome (9%)
  - Eclampsia (2%)
- Gestational diabetes (22% quads, 13% triplets)
- Cesarean section
- Hemorrage requiring blood transfusion
- Acute fatty liver (7% triplets)
- Anemia and other nutritional deficits
- Cholestasis of pregnancy (33% quads, 17% triplets)
- Hyperemesis gravidarum

Chescheir, 2004

TRENDS IN MORTALITY RATES AMONG MULTIPLE BIRTHS

	Singletons			Twins			Triplets or higher		
	White	Black	Ratio	White	Black	Ratio	White	Black	Ratio
Fetal Mortality									
1985–88	6.0	12.0	1.99	24.6	28.3	1.15	36.5	43.6	1.20
1995–98	5.5	12.0	2.19	18.5	27.6	1.51	25.5	60.4	2.37
% change	−9.6	0.5	10.07	−25.7	−2.4	31.80	−29.8	38.6	97.48
Hebdomadal Mortality									
1985–88	3.7	8.6	2.31	29.4	52.5	1.78	91.8	127.9	1.39
1995–98	2.6	6.6	2.58	18.9	36.4	1.91	50.0	88.1	1.76
% change	31.1	−23.5	11.33	35.9	30.5	8.40	−46.7	31.1	29.26
Neonatal Mortality									
1985–88	4.6	10.2	2.21	31.9	57.6	1.70	106.5	158.6	1.50
1995–98	4.1	8.0	2.47	21.9	41.2	1.88	57.3	95.5	1.67
% change	−28.4	21.5	9.68	31.5	−28.5	10.78	−46.2	−38.1	27.96
Infant Mortality									
1985–88	7.5	16.0	2.2	40.9	72.9	1.78	118.9	154.1	1.29
1995–98	5.2	12.3	2.4	26.0	58.6	1.98	63.1	114.8	1.82
% change	−29.8	−23.3	9.2	−36.4	−29.2	11.27	−47.0	−25.0	41.1%

'White' and 'Black' may include persons of Hispanic ethnicity because of the change in birth certificate reporting of race/ethnicity in 1989.
Fetal mortality rate: death in utero 20 weeks' gestation or greater per 1000 live births plus fetal deaths.
Hebdomadal mortality rate: death less than 7 days after live birth per 1000 live births.
Neonatal mortality rate: death less than 28 days after live birth per 1000 live births.
Infant mortality rate: death less than 1 year after live birth per 1000 live births.
Ratio: Black/White rate ratio

Wingate 2006

FETAL RISKS IN HIGH ORDER MULTIPLES

- 100% preterm delivery risk
- High pediatric mortality and morbidity mainly due to premature delivery

Number of fetuses *	GA at delivery (mean weeks)
1	40.0
2	36.5
2 (reduced)	35.5
3	33.0
4	29.5
5	28.0

*Live babies at delivery

Elliot in Multiple Pregnancies; Eds. Blickstein and Keith 2005

OUTCOME OF DELIVERY AT SELECTED WEEKS OF GESTATION

Elliot in Multiple Pregnancies; Eds. Blickstein and Keith 2005

PERINATAL MORTALITY IN UNREDUCED HIGH ORDER MULTIPLE GESTATIONS BY STARTING NUMBER OF EMBRYOS

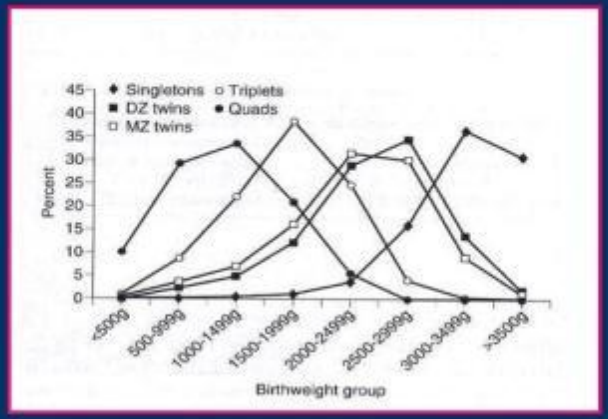
	6	5	4	3
Mansour (1990-97)			40%	33%
Botting (1987)	41%	21.9%	20%	16.4%

GESTATIONAL AGE AT DELIVERY UNREDUCED MULTIPLES

	Average gestational age at birth	*Delivery prior 32 wks*	*Delivery prior 28 wks*
Triplets	33.6 wks (1)	23.0% (1)	8.4% (1)
	33.0 wks (2)	25.3% (2)	8.4% (2)
Quadruplets	31.0 wks (2)	45.0% (2)	14.0% (2)

(1) Dechaud 1998
(2) Stone 2000

BIRTHWEIGHT FREQUENCY DISTRIBUTION IN SINGLETON AND MULTIPLES



Pharoah, 2005

BIRTH WEIGHT SPECIFIC CEREBRAL PALSY PREVALENCE IN SINGLETON AND MULTIPLE BIRTHS

BW	Singletons	Twins	Triplets
	CP prev per 1000 survivors	CP prev per 1000 survivors	CP prev per 1000 survivors
<1500 g	68.4	60.5	47.1
1500- 2499 g	10.4	9.5	10.3
>/= 2500 g	1.4	3.4	0
All BW	2.1	9.7	20.7

Pharoah, 2006

SOCIETY FINANCIAL COST OF MULTIPLE PREGNANCIES*

Daily hospital charge for both mother and neonate

Singleton	$ 591
Twin	$ 996
High- order	$ 1,715

* *In addition to the personal financial risks*

Ultrasound Obstet. Gynecol. 4 (1994) 339–341

An approach to multifetal pregnancy reduction in a pregnancy of grand order (12 fetuses)

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Key words: MULTIFETAL PREGNANCY, MULTIFETAL PREGNANCY REDUCTION, TRANSVAGINAL SONOGRAPHY

ABSTRACT

Our objective was to determine the best method to approach a multifetal pregnancy reduction of a patient with a multiple pregnancy of grand order (12 fetuses). Transvaginal ultrasound-guided reduction was performed in three stages. Successful outcome was achieved. The patient delivered twins at 37 weeks' gestation. The published and unpublished literature is reviewed and discussed in the light of this case. Our conclusion is that a multifetal pregnancy reduction of grand order can be performed in stages to achieve the desired number of fetuses.

citrate and Pergonal® (Serono Laboratories Inc.) stimulation of the ovaries, respectively, resulting in normal deliveries of singleton infants. The index pregnancy was the result of Pergonal stimulation with a total of eight ampules. On day 7, the estradiol level was 557 pg/ml and on day 11 it reached 1836 pg/ml. Transvaginal sonography revealed 14 follicles in the right and 13 in the left ovary. The endometrial thickness was 13 mm. On this day, the patient received Synarel® (Syntex) nasal spray. Ovulation occurred on day 12 and intrauterine insemi-

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Fetal reduction in a nontuplet pregnancy: technical and ethical considerations

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Abstract

A case of a nontuplet pregnancy that was successfully reduced to twins resulting in a good neonatal outcome is described. A 37-year-old woman achieved a nontuplet pregnancy after ovarian stimulation with GnRH analogues and gonadotrophins in the short protocol and artificial insemination. Reduction of the nontuplet pregnancy to twins was successfully performed in three attempts and delivery by caesarian section was followed on the 32nd week of pregnancy. Two alive and healthy neonates with birth weights 1235 g and 1515 g were born. Multifetal pregnancy reduction is medically justified in the very high order pregnancies. The first approach, though, to the problem of multiple gestation should be prevention through carefully monitored infertility treatment, as the elective embryo reduction procedure carries with it medical, ethical and psychological issues for both the parents and the physicians involved.

MAIN GOAL OF MULTIFETAL PREGNANCY REDUCTION

- To decrease premature delivery rates
- Reduce mortality in premature deliveries
- To decrease the rate of severe prematurity
- To decrease neurodevelopmental handicaps
- To reduce the risk of maternal complications

IMPACT OF MFPR

- MFPR does not reduce the risk of loss of the entire pregnancy before 24 wks
- MFPR may increase the risk of a second trimester miscarriage by 1- 2%
- MFPR is a distressing experience for parents
- Maternal distress may have/not have long-term adverse effects on women's psychological well-being

MULTIFETAL PREGNANCY REDUCTION: THE CONSEQUENTIALIST APPROACH

When faced with a potentially disastrous situation, one must act to bring about the greatest good for the greatest number of people.
Thus killing of some fetuses is justified, so that the pregnancy may result in one or two healthy babies with less risk to the mother...

Gallagher, 1995

OBJECTION TO MULTIFETAL PREGNANCY REDUCTION

- Religious
- Ethical
- Legal
- Psychological issues

MULTIFETAL PREGNANCY REDUCTION

"....non selective embryo reduction should be viewed as a response to an unforeseen and unavoidable contingency, not a routinely accepted treatment for an iatrogenic problem..."

ACOG 1999

OUTCOME IN REDUCED & UNREDUCED TRIPLETS

		Gestational age at delivery			
	Total	*Mean(wks)*	*<37(wks)*	*<32(wks)*	*<28(wks)*
Natural history	442	33	88%	29%	10
Triplets reduced	81	36.1	41%	5%	none

Berkowitz, 1993

STRONG INVERSE CORRELATION BETWEEN STARTING NUMBER AND THE LOSS RATE FOLLOWING THE REDUCTION PROCEDURE

	>/=5	*4*	*3*	*2*
Stephen (2000)	25%	23.6%	15%	0%
Evans (2001)	17.9%	12.2%	6.5%	5.8%
Evans (2001) >'94		13%	5.1%	
Evans (2001) '95-'98		6.6%	4.4%	
Stone (2002)	6.3%	5.4%	5.3%	2.5%
Lipitz (2001) at 11-12 wks			4.3%	
Lipitz (2001) at 13-14 wks			4.0%	

MFPR: PREGNANCY LOSSES & VERY PREMATURE DELIVERY* ACCORDING TO STARTING NUMBER

* 25- 28 weeks

Evans et al., Am J Ob Gyn 2001

TIMING OF PREGNANCY LOSSES AFTER MFPR

Fasouliotis (1997)	33% of losses </= 4 wks
	66.6% of losses > 4 wks, <24 wks
Stephen (2000)	5.5% lost at<16 wks
	13.6% lost at >16<24 wks
	5.9% lost at 25- 28 wks
Sebire (1997)	50% of losses =5 wks
Stone (2002)	14.8% of losses < 4wks
	29.6% of losses 4- 8 wks
	55.6% of losses >8 wks

OVERALL PREGNANCY LOSS RATE AFTER MFPR BY ENDING NUMBER

	3	*2*	*1*
Stephen (2000)	45.5%	19.4%	10.8%
Evans (2001)	19.5%	10.2%	10.2%
Stone (2002)	16.7%	5.5%	3.4%

MFPR: PREGNANCY LOSSES & DELIVERIES ACCORDING TO FINISHING NUMBER

Evans et al., Am J Ob Gyn 2001

FIRST TRIMESTER PROCEDURE

- The "vanishing twin" phenomenon has to be considered (48% of multiple fetuses diagnosed by TV US at 5- 6 wks vanished at 12.0 wks, Blumenfeld et al. 1992)
- The "appearing fetus" phenomenon, has to be considered (11% of dichorionic, 86% of monochorionic, 16% of high order multiples were undercounted at 5.0- 5.9 wks, Doubilet et al. 1998)

PRENATAL DIAGNOSIS & HIGH ORDER MULTIPLES

Are more than additive risks of karyotyping by either 2nd trimester amniocentesis or CVS before or after MFPR?

What is the success rate of CVS prior to MFPR at 10- 13 weeks gestation?

How well do traditional serum screening studies work in women with high order multiples following reduction?

How well do first trimester ultrasounds work in high order multiples prior to embryo reduction?

Is there a reasonable trade off between risks of the reduction versus additional sonographic information if one delays fetal reduction past 13 weeks of gestation?

Chescheir, 2004

THE CHOICE OF WHICH FETUSES TO REDUCE

- Fetuses easiest to reach with the needle
- Fetuses furthest from the internal os
- Fetuses with the smallest crown- rump length
- Fetuses with cardiac frequency alterations
- Fetuses with a suspicion of a malformation on ultrasound examination
- Enlarged NT?

Fetuses with abnormal karyotype (after CVS)

OPTIONS OF INVASIVE PRENATAL DIAGNOSIS BEFORE MULTIFETAL PREGNANCY REDUCTION

- To have no testing and to take the chance of bearing a chromosomally abnormal child
- To undergo a traditional midtrimester amniocentesis after the multifetal pregnancy reduction procedure
- To undergo CVS before multifetal pregnancy reduction to ensure that the fetuses remaining after the procedure are chromosomally normal
- NT and anatomy scan before procedure!!!

NT AND EMBRYO REDUCTION AT 11 WEEKS OF GESTATION IN QUADRUPLETS

	Fetus 1	Fetus 2	Fetus 3	Fetus 4
CRL (mm)	44.7	44.2	45.8	44.4
NT (mm)	0.7	0.9	2.3	0.9
Estimated risk	1 in 1809	1 in 1830	1 in 210	1 in 1806
Karyotype	46, XY*	46, XX *	47, XX +21**	46, XY**

* *AF at 15 weeks*
** *AF and FBS at 11 weeks before ER*

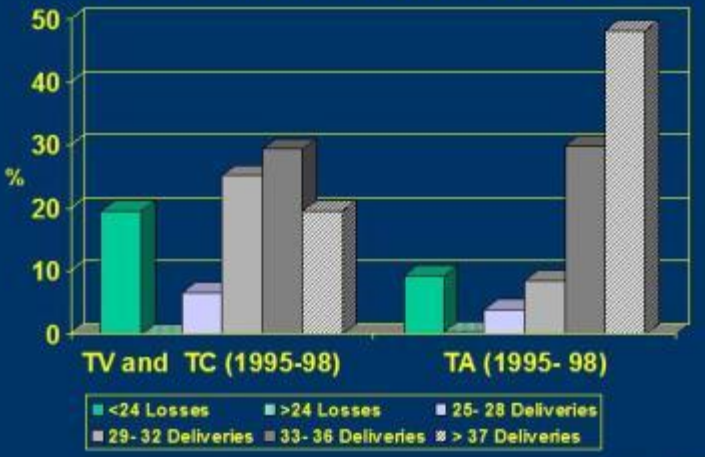
Monni, Ultrasound Obstet Gynecol 1999

HOM - MFPR

- Transvaginal / Transabdominal guided procedures
- First trimester (8 wks transvaginal, 10- 12 wks transabdominal)
- 1 session or more*
- Injection of 0,5 ml potassium chloride (KCL) into the area of the fetal heart, with a 21 gauge needle, guided by the US probe. The heart activity stops within 1 min after each injection.
- A rescan planned after 1- 2 hours
- If the heart beats, repeat the procedure in the same fetus
- Bed rest, antibiotics and progesterone

* The following sessions are planned in 5- 13 days apart

MFPR: PREGNANCY LOSSES & DELIVERIES ACCORDING TO TRANSVAGINAL OR TRANSCERVICAL VERSUS TRANSABDOMINAL ROUTE



Evans et al., Am J Ob Gyn 2001

MFPR in HOM: PRACTICAL QUESTIONS

- What is the largest number of fetuses that can be reduced with good outcome for a singleton or twin pregnancy?
- If more than 4 fetuses are to be reduced, should the procedure be performed in stages, and if so, how many?
- If a MFPR of a high order is performed, does this have any bearing on the maternal coagulation profile?

HOM MFPR EXPERIENCE

	Starting fetuses	*Sessions*	*Ending fetuses*
Farquhart (1988)	5	2	2
Evans (unpublished)	8	1 (6)	2
	8	2	2
Lynch (unpublished)	7	2	2
	7	2	2
	9	3 (3-3-1)	2
Monteagudo (1994)	12	3 (4-4-2)	2

HOM REDUCTION IN CAGLIARI CENTRE PERSONAL EXPERIENCE

30 Multiples - 153 Fetuses

Starting No.	No.	No. procedures	No. Losses
9	1	2	-
8	1	2	-
7	3	1- 2	-
6	5	2	-
5	5	1	4
4	15	1	5
153 Fetuses	30 Multiples		

HOM MFPR experience in Cagliari

9-8-7-6- PLETS

Starting No.	Obtained by	Procedures	Therapy	Outcomes	Delivery wks
9	TVI	2	Yes	2 A&W	36 wks
8	IUI	2	Yes	2 A&W	35 wks
7	IUI	1	Yes	3 A&W	35 wks
7	IUI	2	Yes	2 A&W	37 wks
7	IUI	2	Yes	2 A&W	35 wks
6	TVI	2	Yes	2 A&W	35 wks
6	IUI	2	Yes	2 A&W	37 wks
6	IUI	2	Yes	2 A&W	37 wks
6	IVF	2	Yes	Pregnancy loss	-
6	IVF	2	Yes	Pregnancy loss	-

HOM MFPR experience in Cagliari

5 - PLETS

Starting No.	Obtained by	Procedures	Therapy	Outcomes	Delivery
5	IUI	1	Yes	2 A&W	36 wks
5	IVF	1	Yes	2 A&W	27 wks
5	IUI	1	Yes	2 A&W	36 wks
5	IUI	1	Yes	Pregnancy loss 20 wks	-
5	IUI	1	Yes	Pregnancy loss 19 wks PPROM	-

HOM MFPR experience in Cagliari

4- PLETS

Starting No.	Obtained by	Procedures	Therapy	Outcomes	Delivery wks
4	IUI	1	Yes	2 A&W	37 wks
4	IUI	1	Yes	2 A&W	36 wks
4	IUI	1	Yes	2 A&W	34 wks
4	TVI	1	Yes	2 A&W	36 wks
4	IVF	1	Yes	2 A&W	38 wks
4	IUI	1	Yes	1 A&W 1 IUD 18 wks Spina biphida	37 wks
4	COH CC	1	Yes	2 A&W	37 wks
4	IVF	1	Yes	2 A&W	36 wks
4	IUI	1	Yes	IUD 20 wks	-
4	IVF	1	Yes	Pregnancy loss	-
4	IUI	1	Yes	1	35 wks
4	IUI	1	Yes	1	36 wks
4	IUI	1	Yes	2	36 wks
4	IUI	1	Yes	2	Ongoing
4	IUI	1	Yes	2	Ongoing

HOM MFPR: PRACTICE

- Coagulation is not influenced, except for the fibrinogen, that decrease in 3 weeks after the procedure
- Counting the exact number of sacs/fetuses is very difficult,especially when it reaches eight or nine
- 3-D ultrasound could be of help
- In MFPR of grand order it would be the best approach to reduce 4 to 5 fetuses at the initial procedure and rescan several days later to count more accurately the remaining fetal heart beats
- Day hospital procedure, home bed rest,antibiotics

CONCLUSIONS (1)

- MFPR: mapping scan is critical, determine chorionicity early!
- Can be performed by TA & TV route
- If possible prefer the TA route
- Consider NT & anatomy scan before MFPR
- Prenatal testing safe before (CVS) & after (amnio)
- Consider performing at 12-13 wks
- Loss rates commensurate with experience
- Loss rates increase with increased starting and finishing number

I. TIMOR TRITSCH

CONCLUSIONS (2)

- MFPR reduces delivery of VLBW & LBW and handicapped (CP) infants!!
- There is a probability of an inflammatory process following MFPR
- IUGFR may be present if staring # is ≥ 5
- DIC is not an issue
- MS αFP after MFPR irrelevant
- CRL discrepancy >5 mm. predictive of discordancy

I. TIMOR TRITSCH

CONCLUSIONS (3)

- No long lasting psychological sequelae
- If monochorionic pair in triplet or higher MFP, reduce mono' twin pairs
- MFPR saves money to society & the family
- Cervical length not different in reduced and nonreduced twins
- There is evidence that MFPR from HOM to twins is justified
- HOM MFPR: is medically indicated & supported by the literature (CP!!)

I. TIMOR TRITSCH