NOVEL AVENUES IN ART

2nd annual meeting of Baltic Fertility Society

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Prof. D. Feldberg

Vice Chairman Helen Schneider Hospital for Women,
Rabin Medical Center and Sackler School of Medicine,
Tel Aviv University, Tel Aviv, Israel

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Congenital Malformations in Children Born after ART Including Imprinted Gene Defects

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Tel Aviv University, Tel Aviv, Israel

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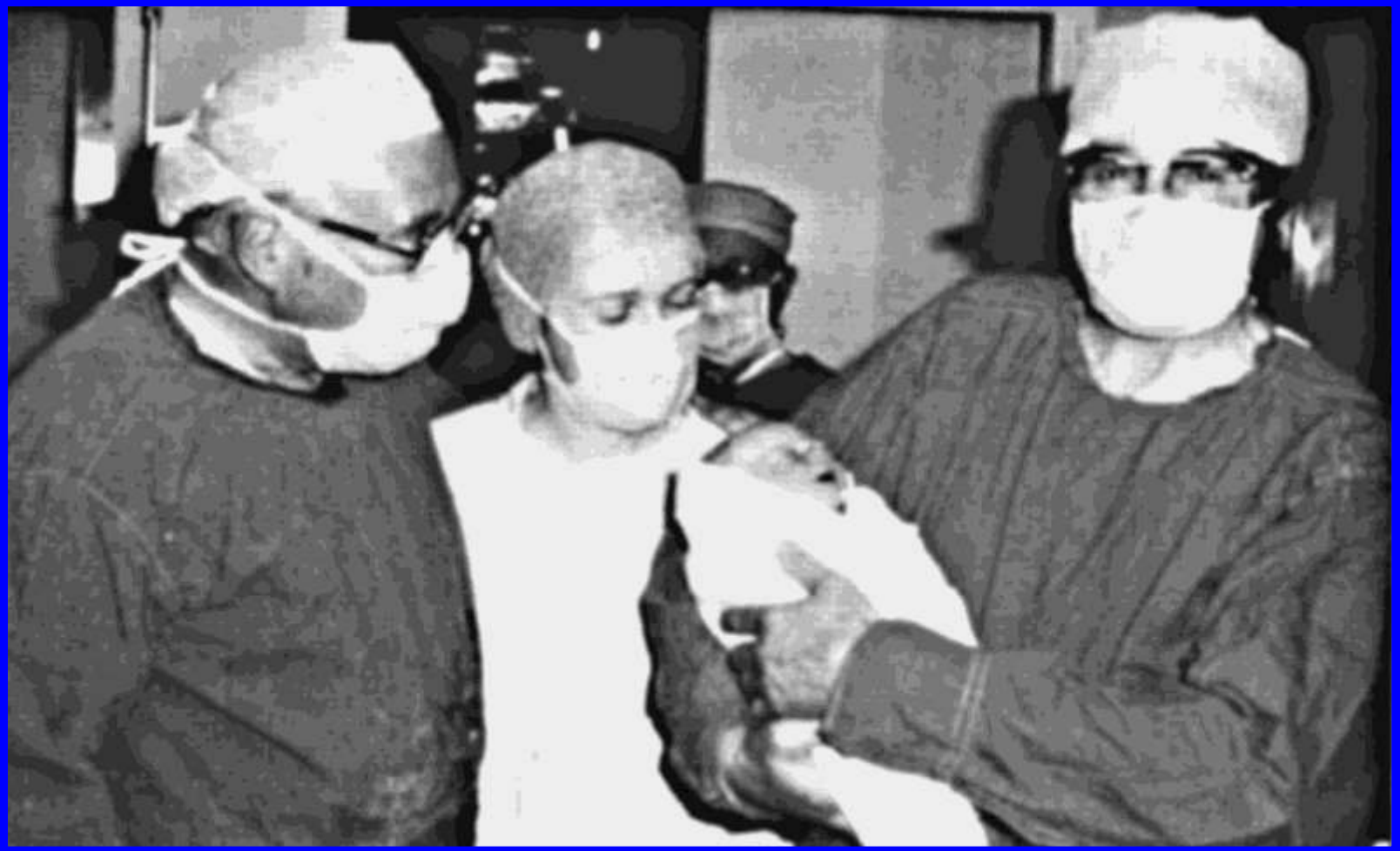
Prof. Y. Verlinsky
1943 - 2009

STEPTOE, EDWARDS, LOUISE BROWN
25 JULY 1978



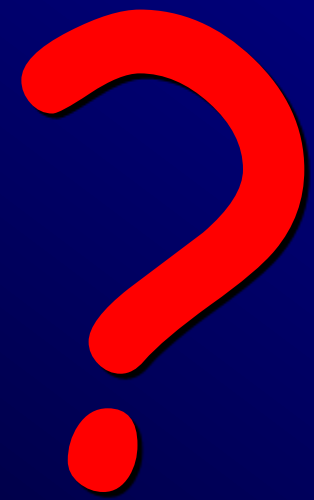
World Availability of Treatment

1978 → 1990 over 200,000 babies

1991 → 2014 over 6,000,000 babies

Were born from ART all over the world

If IVF is an Appropriate Solution-are ART Children Healthy



Evolution of Pregnancies and Initial Follow-Up of Newborns Delivered After ICSI

Palermo G. D. et al

JAMA 276 ; 1893-1897, 1996

Congenital Malformations - Intracytoplasmic Sperm Injection (ICSI) vs in Vitro Fertilization (IVF)

	ICSI	IVF
Cycles. No.	987	2878
Offsprings delivered No.	578	653
Newborns with major malformations No. (%)	9(1.6)*	23(3.5)*
Newborns with minor malformations No. (%)	6(1.0)#	20(3.1)#
Total malformation No. (%)	15(2.8)$	43(6.6)$

* # $ p=NS

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Conclusions

Our results demonstrate that the evolution of pregnancies and the occurrence of congenital malformations following treatment by ICSI, are similar to outcomes with other Assisted Reproductive Technologies

Neonatal Data on a Cohort of 2889 Infants Born After ICSI (1991-1999) and of 2995 Infants Born After IVF (1983-1999)

Bonduelle M. et al

Human Reprod. 17:671-694, 2002

Major and minor malformations

	No. of children	Major malformation N (%)	Minor malformation N (%)	Minor malformation only	Major With minor
ICSI					
Singletons	1499	46 (3.06[b])	97 (6.47)	84	13
Multiples	1341	50 (3.65[b])	83 (6.18)	76	7
Twins	1288	45 (3.49)	75 (5.82)	68	7
Triplets	113	5 (4.42)	8 (7.07)	8	-
Total	2840	96 (3.38[b])	180 (6.34[c])	160	20
IVF					
Singletons	1556	50 (3.21[b])	122 (7.84)	119	3
Multiples	1399	63 (4.50[b])	173 (12.36)	159	14
Twins	1250	55 (4.40)	138 (11.4)	129	9
Triplets	145	8 (5.51)	35 (24.13)	30	5
Total	2955	112 (3.79[a])	295 (9.98[c])	278	17

[A] Cohran Mantel-Haenzel test P= not significant (0.402); not more major malformations in ICSI or IVF

[b] Cohran Mantel-Haenzel test P= (0.046); more major malformations in multiples versus singletons in ICSI or IVF

[C] Fisher's exact test P<0.001; more minor malformations in IVF than ICSI

Major malformations in ICSI children in relation to sperm origin

	Total no. of children	Major Malformation (N)	Major Malformation (%)
Ejaculated	2477	84	3.39[a,b,c]
Non-ejaculated	311	10	3.21[a]
Testicular	206	6	2.91[cd]
Fine needle aspiration (FNA)	51	2	
Surgical biopsy	154	4	
FNA and biopsy	1	0	
Epididymal	105	4	3.80[bd]
Donor sperm	52	0	0
Total	2840	96	3.38

Major malformations rate per organ system in ICSI versus IVF in lives births

System	ICSI			IVF		
	Major Malformation per system N =2480	(%) of total	0% of malformation	Major malformation per system N=2955	(%) of total	0% of malformation
Cardiac	30	1.06	31.9	44	1.49	40.0
Cleft lip/palate	6	0.21	6.4	6	0.20	5.4
Ear, eye	1	0.03	1.1	1	0.03	0.9
Gastrointestinal	3	00.10	3.0	10	0.33	9.1
Genital	11	0.387	11.7	21	0.71	19.1
Metabolic	2	0.07	2.1	2	0.06	1.8
Musculoskeletal	23	0.80	24.5	12	0.40	11.0
Nervous	12	0.42	12.8	6	0.20	5.4
Respiratory	0	0	0	1	0.03	0.9
Urinary	7	0.24	7.4	7	0.24	6.4
Total	95		100	110		100

[C] Fisher's exact test comparing ICSI and IVF for each system were all not significant

Conclusions

This study shows that pregnancy outcome after ICSI is similar to that for IVF. No greater miscarriage rate, stillbirth rate or perinatal death rate occurred among the ICSI pregnancies.

Neonatal outcome, health of the ICSI children and major malformation rates are comparable among both ICSI and IVF children.

Conclusions

Among the ICSI children, we **did not observe** any **increase** in the general **major malformation rates** in **liveborns** or in to the total malformation rates, the ICD 10 codes or the **minor malformation** rates.

No differences in major malformation rates were observed in the different organ systems in ICSI compared to IVF. Sperm quality or sperm origin does not appear to play a role in the outcome of ICSI children

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The Risk of Major Birth Defects After ICSI and IVF

Hansen M. et al

N. Eng. J. Med 10:725-730,2002

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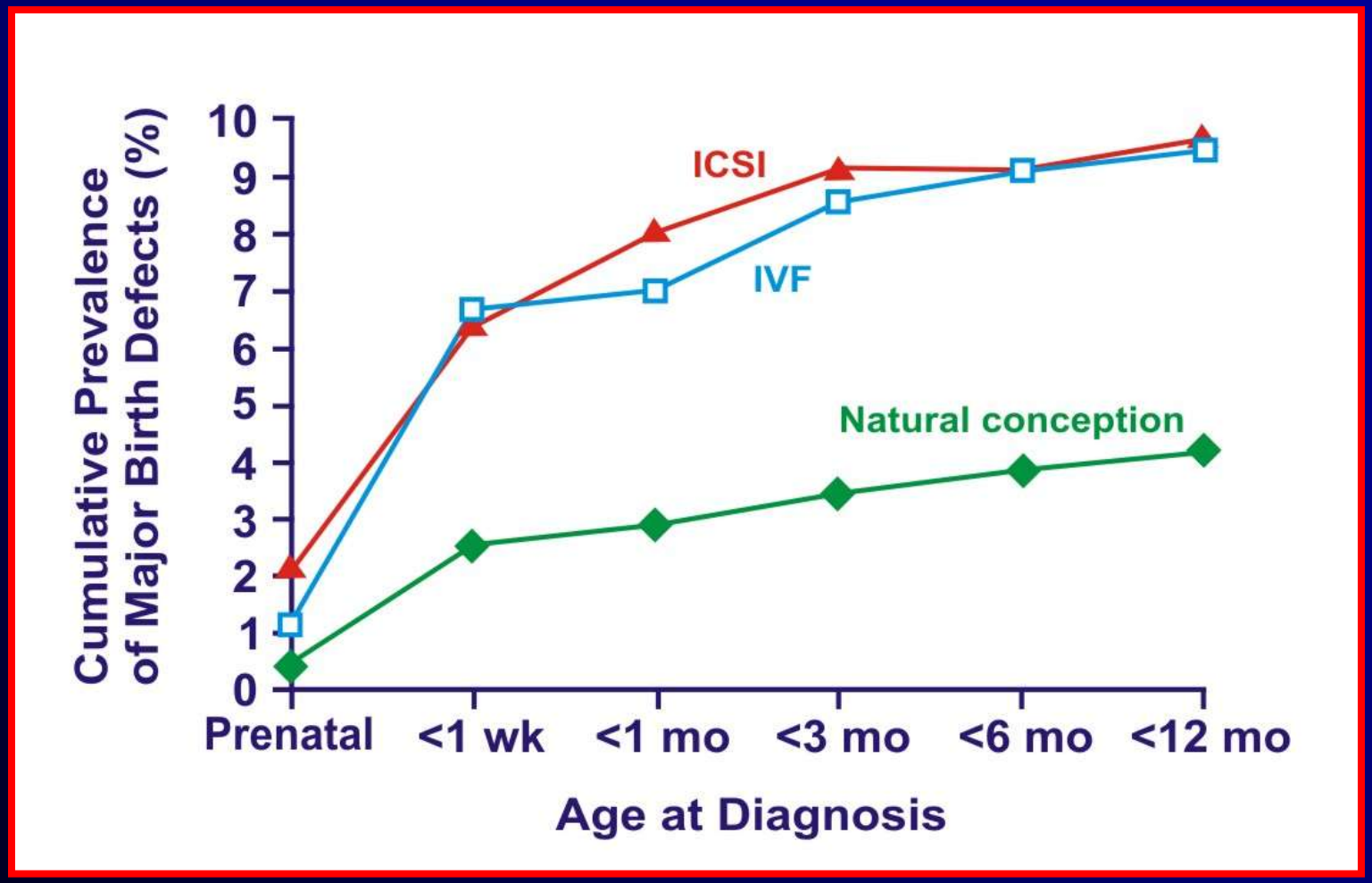
Cumulative Prevalence of Major Birth Defects in Singeltons



Prevalence of major birth defects according to the organ system affected

Type of major defect	All infants					Singletons only				
	ICSI (n=301) No. %	P Value	IVF N=837) No. %	P Value	Natural Conception (n=4000) No. %	ICSI (n=301) No. %	P Value	IVF N=837) No. %	P Value	Natural Conception (n=4000) No. %
Any	26 (8.6)	<0.001	75 (9.0)	<0.001	168 (4.2)	18 (9.7)	<0.001	50(9.5)	<0.001	164 (4.2)
Cardiovascular	4 (1.3)		15 (1.8)	<0.001	24 (0.6)	3 (1.6)		7 (1.3)		24 (0.6)
Urogenital	7 (2.3)		22 (2.6)	0.01	54 (1.4)	5 (2.7)		14 (2.7)	0.03	52 (1.3)
Musculoskeletal	10 (3.3)	0.004	28 (3.3)	<0.001	45 (1.1)	5 (2.7)	0.004	20 (3.8)	<0.001	44 (1.1)
Gastrointestinal	3 (1.0)		5 (0.6)		25 (0.6)	2 (1.1)		2 (0.4)		24 (0.6)
Central nervous System	0		3 (0.4)		6 (0.2)	0		2 (0.4)		6 (0.2)
Chromosomal	3 (1.0)	0.05	6 (0.7)	0.03	9 (0.2)	3 (1.6)	0.02	3 (0.6)		9 (0.2)
Metabolic	1 (0.3)		2 (0.2)		4 (0.1)	0		1 (0.2)		4 (0.1)
Other	2 (0.7)		21 (2.5)	<0.001	25 (0.6)	2 (1.1)		15 (2.8)	<0.001	25 (0.6)

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Conclusions

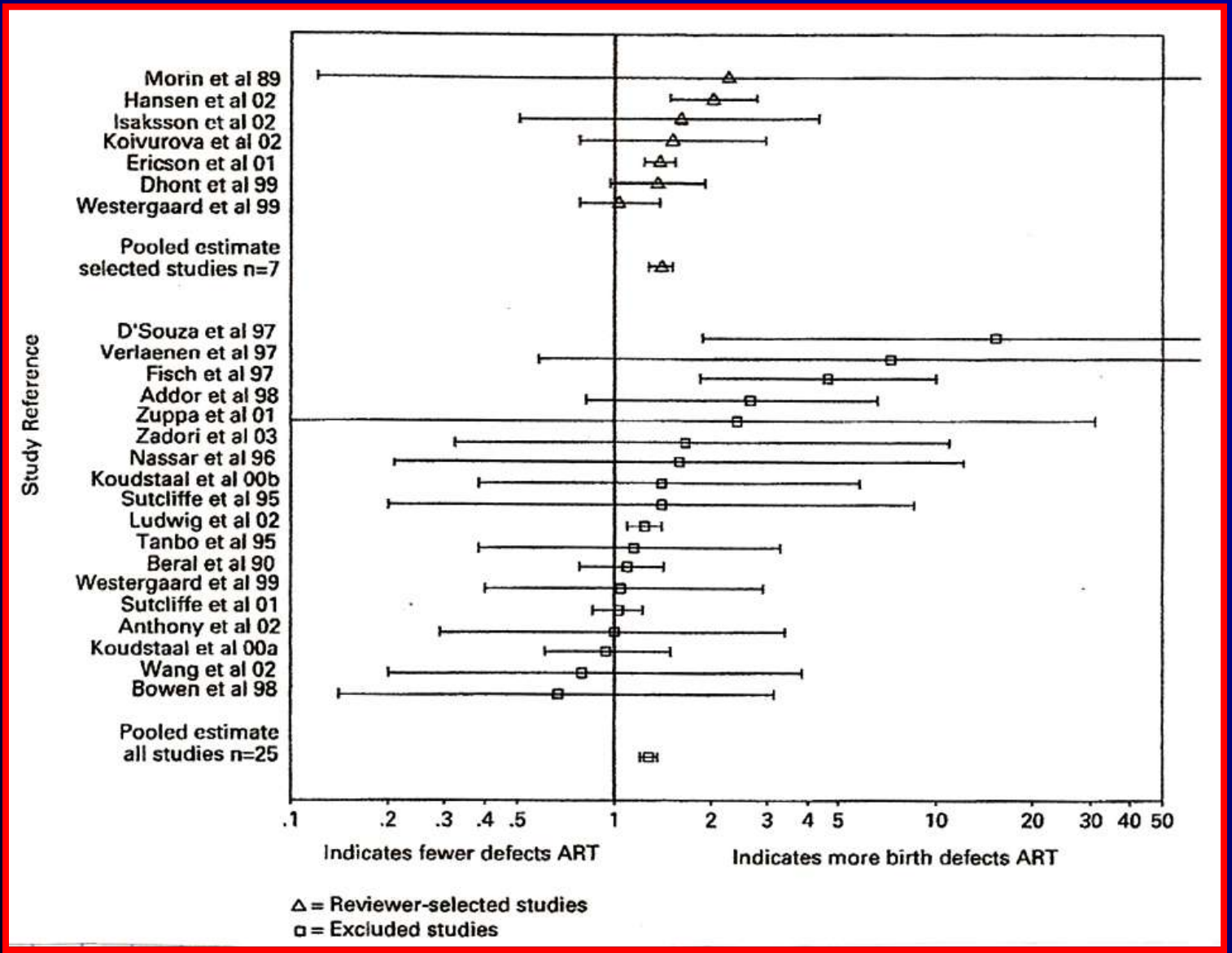
Although the prevalence of a specific defect is rarely reported for infants conceived with ART, other authors have also suggested that the prevalence of these defects is increased among ART infants

Assisted Reproductive Technologies and the Risk of Birth Defects – A Systematic Review

Hansen M. et al

Human Reprod. 20:328-338, 2005

Meta-analysis of reviewers selected studies



Conclusions

The results of our systematic review and meta-analyses suggest that infants following ART treatment are at increased risk of birth defects, compared to spontaneously conceived infants.

This information should be made available to couples seeking ART treatment. Larger, population-based studies are now needed to address questions of aetiology, so we can provide better information for counseling patients prospectively

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Obstetric Outcomes and Congenital Abnormalities after IVF, IVM and ICSI

Buckett W.M. et al

Obstet. Gynecol. 4: 885-891, 2007

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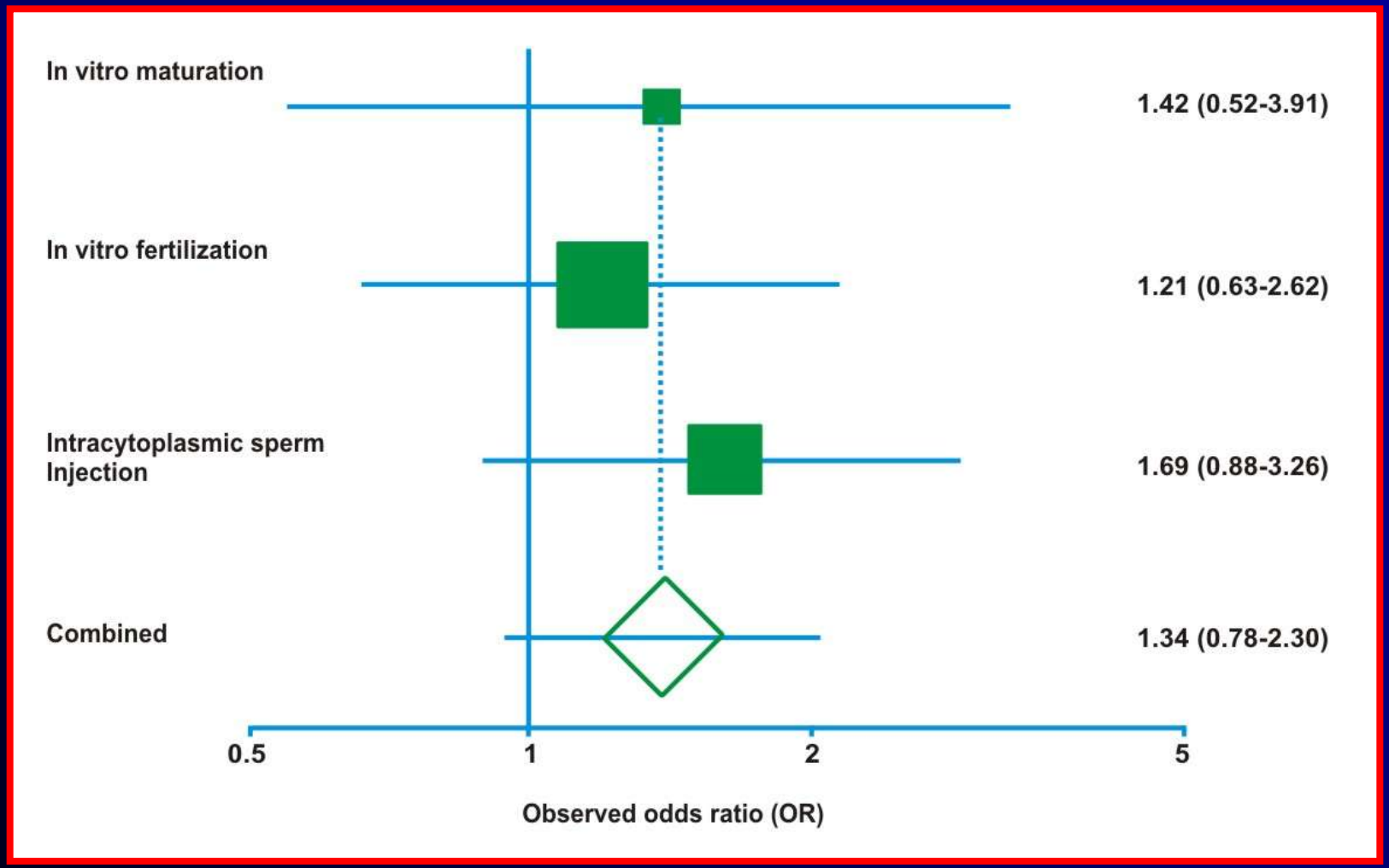
Observed odds ratio for any congenital abnormality after conception with IVM, IVF and ICSI



Comparison of Outcomes in Singleton Pregnancies Conceived After In Vitro Maturation, In Vitro Fertilization, or Intracytoplasmic Sperm Injection With Spontaneously Age - and Parity – Matched Controls

	IVM (n=31)	IVF (n=133)	ICSI (n=104)	Controls (n=338)	P (vs controls)
Mean birth weight (g)	3,482*	3,209	3,163	3,260	0.48*
Proportion LBW (less than 2,500 g)	1/31(3)	14/133(10)	15/104 (14)	30/338(9)	NS
Proportion VLBW (less than 1,500 g)	0/31(0)	1/133(1)	3/104(3)	8/350(2)	NS
Proportion of macrosomic infants (more than 4,200 g)	3/31(10)	5/133(4)	2/104(2)	12/338(4)	NS
Mean gestational age (wk+d)	39+3	38+3*	38+0*	39+6	<.001*
Proportion delivery less than 37 wk	2/31(6)	23/133(17)*	25/104(24)*	18/338(5)	<.01*
Proportion delivery less than 34 wk	0/31(0)	5/133(4)	8/104(8)	4/338(2)	NS

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Conclusions

All ART pregnancies are associated with an increased risk of multiple pregnancy, cesarean delivery and congenital anomalies associated with any additional risk.
Compared with IVF and ICSI, IVM is not associated with any additional risk

Rare Congenital Disorders, Imprinted Genes and Assisted Reproductive Technology

Gosden R. et al

Lancet 361:1975-1977, 2003

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Safety of Assisted Reproductive Technologies

A possible link has now been made between **ART** conception and certain congenital abnormalities, notably **Beckwith-Wiedemann Syndrome**.
This neonates have abnormalities at **chromosome 11p 15** associated with **organ overgrowth** and **abdominal wall defects**, as well as increased risk of **embryonal tumors**

Safety of Assisted Reproductive Technologies

Some reports has shown association between **Angelman Syndrome** and **ICSI**.
This syndrome is characterized by severe **mental retardation, motor defects, lack of speech** and a happy disposition and is linked with a **loss of function** of the maternal **allele of UBE3A**

Imprinted Genes in Development

Both **Angelman** and **Beckwith – Wiedemann** syndromes are associated with **imprinted gene clusters**. About 50 genes are differently expressed according to their origin in either the oocyte or spermatozoon.

These imprinted genes have role in growth and development as well as in tumor suppression.

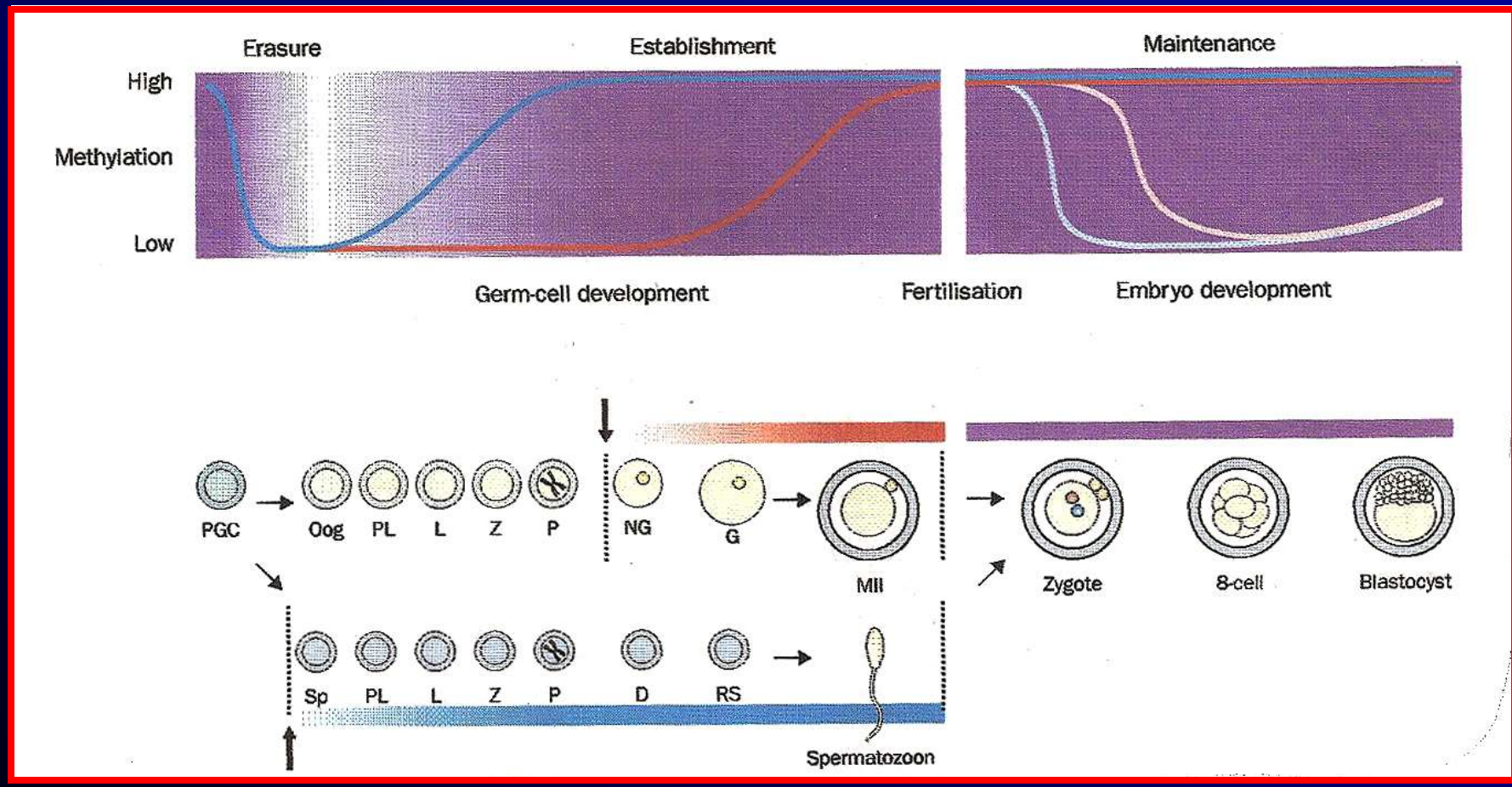
By definition, at imprinted loci, only one allele is active (maternal or paternal) and the inactive one is **epigenetically** marked by **histone modification cytosine methylation or both**

Case of apparent imprinted gene diseases associated with Assisted Reproductive Technology (ART)

Syndrome	Causes number	ART	Loss of imprinting (gene)	Country	Reference
Cases with analysis of underlying imprinting defect					
Beckwith-Wiedemann	6	IVF and ICSI	KCNQ10T1	UK	7
	7	IVF and ICSI	KCNQ10T1 and H19	USA	6
Angelman	6	IVF and ICSI	KCNQ10T1	France	8
	1	ICSI	SNRPN	Norway	9
	2	ICSI	SNRPN	Germany	10
Cases without analysis of Underlying imprinting defect					
Beckwith-Wiedemann	1	ICSI		Belgium	2
	1	IVF and ICSI		-	11
	1	IVF and ICSI		-	12
	1	IVF		Netherlands	13
	1	IVF		UK	14

IVF = in vitro fertilization. ICSI = intracytoplasmic sperm injection.

Programmed demethylation and methylation of genomes of developing oocytes, spermatozoa and embryos



Conclusions

The epidemiological evidence associating Beckwith-Wiedemann syndrome or Angelman syndrome with ART procedures is still tentative and does not yet established a causal link.

The absolute risks are small and unlikely to deter would-be parents from using the technology. Prospective longitudinal studies of children born after ART in multicentric formate with follow-up of physical, neurobehavioral and cancer incidence are needed

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Are Children Born After ART at Increased Risk of Adverse Health Outcomes ?

Shieve L. A. et al

Obstet. Gynecol. 103:1154-1163, 2004

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Imprinting Disorders

Recently, there has been concern that **ART may lead to abnormalities in imprinting and possible association between ART and Beckwith-Wiedemann and Angelman syndromes**

Imprinting Disorders

Additionally, cases of Beckwith-Wiedemann and Angelman syndromes secondary to a sporadic imprinting defect on the maternal chromosome have been reported among children conceived by ICSI. Finally, studies of mammalian embryos, including sheep and mouse, also have suggested a link between In Vitro culture and imprinting anomalies

Conclusions

In children conceived with ART who represent an at-risk subgroup with the need for screening, a special system of follow up may emerge. More rigorous research is needed to identify areas where ART treatment could be improved in ways that may lead to decreased risks for some outcomes

Assisted Reproductive Technology and Congenital Overgrowth: Some Speculations on a Case of Pallister-Killian Syndrome

Chiurazzi P. et al

Am. J. of Med. Genetics, 130-A:315-316, 2004

Discussion

It is possible that fetal overgrowth is reflecting a favorable balance of hormones and / or growth factors capable of contrasting the growth - restricting effect of ART.

For instance, decreased levels of the placental protein 14 (PP14) reported in the first trimester of pregnancies achieved by ART have been linked to Intra Uterine Growth Retardation. Thus the tendency to over growth could counteract the tendency of fetuses conceived by ART to be a low or very low birth weight

Conclusions

If this explanation is correct, one should speculate that the tendency to overgrowth by whatever chromosome imbalance or imprinting defect, may protect the fetus from the opposing tendency to Low Birth Weight associated with ART

Growth and Development of Children Born After IVF

Ceelen M. et al

Fertil. & Steril. 90:1662-1673, 2008

Biological Factors Known to Influence Prenatal Growth and Development

Intrinsic Factors

Fetal factors:
- Chromosomal disorders
- Chronic fetal infections
- Congenital malformations
- Genetic variation

Extrinsic Factors

Maternal factors:

**** Before pregnancy:***
- Stature and pre-pregnancy weight
- Age and parity
- Periconceptional nutritional status (e.g. folate status)

**** During pregnancy:***
- Cardiovascular illness (e.g. (pre-)eclampsia, diabetes, renal disease)
- Decreased 0^2 availability (e.g. severe anemia, high altitude)
- Poor maternal nutrition
- Smoking
- Use of alcohol, medication or other chemical agents

Uterine and Placental factors:
- Placental insufficiency
- Abnormal placentation
- Multiple pregnancies

Epigenetic Defects

Recently a biological mechanism called **genomic imprinting** and its potential link to **IVF-related health** problems has become a **topic of major interest**.

Genomic imprinting, an inherited **epigenetic form of gene regulation**, has been increasingly recognized as one of the **key determinants** for **normal intrauterine development**

Epigenetic Defects

A significant number of **imprinted genes** appear to have important roles in **embryonic/fetal growth and placental function**. At imprinted loci, only one of the **paternal alleles is active**, transcription of the inactive allele is **repressed due to epigenetic marks by histone** modification or **cytosine methylation** according to **parental origin**

Molecular Details of Studies on Angelman Syndrome (AS) and Beckwith-Wiedemann Syndrome (BWS) Diagnosed in ART Children

Angelman Syndrome

- Severe mental retardation, motor defects, lack of speech and happy disposition
- Incidence: 1/15,000 newborns
- <5% of cases due to imprinting defect

	ART children with AS	Loss of methylation at SNRPN locus (cases/number tested)
Cox et al.	2	2/2
Orstavik et al.	1	1/1

Molecular Details of Studies on Angelman Syndrome (AS) and Beckwith-Wiedemann Syndrome (BWS) Diagnosed in ART Children

Beckwith-Wiedemann Syndrome

- Somatic overgrowth, congenital malformations and predisposition to embryonic neoplasia
- Incidence: ~1/14,000 newborns
- 50-60% of cases due to imprinting defect

	ART children in BWS cohort	Loss of methylation at KvDMR1 locus (cases/number tested)
DeBaun et al.	7 3/65	5/6
Maher et al.	6/149	2/2
Gicquel et al.	6/149	6/6
Halliday et al.	4/37	3/3
Sutcliffe et al.	11	8/8

Conclusions

To elucidate whether children born after IVF are at increased risk for environmentally induced epigenetic modifications during early prenatal development. Including long-lasting consequences in postnatal life and perhaps adult life. Casual pathways between IVF-related health problems and early prenatal epigenetic programming should be investigated and unraveled

Conclusions

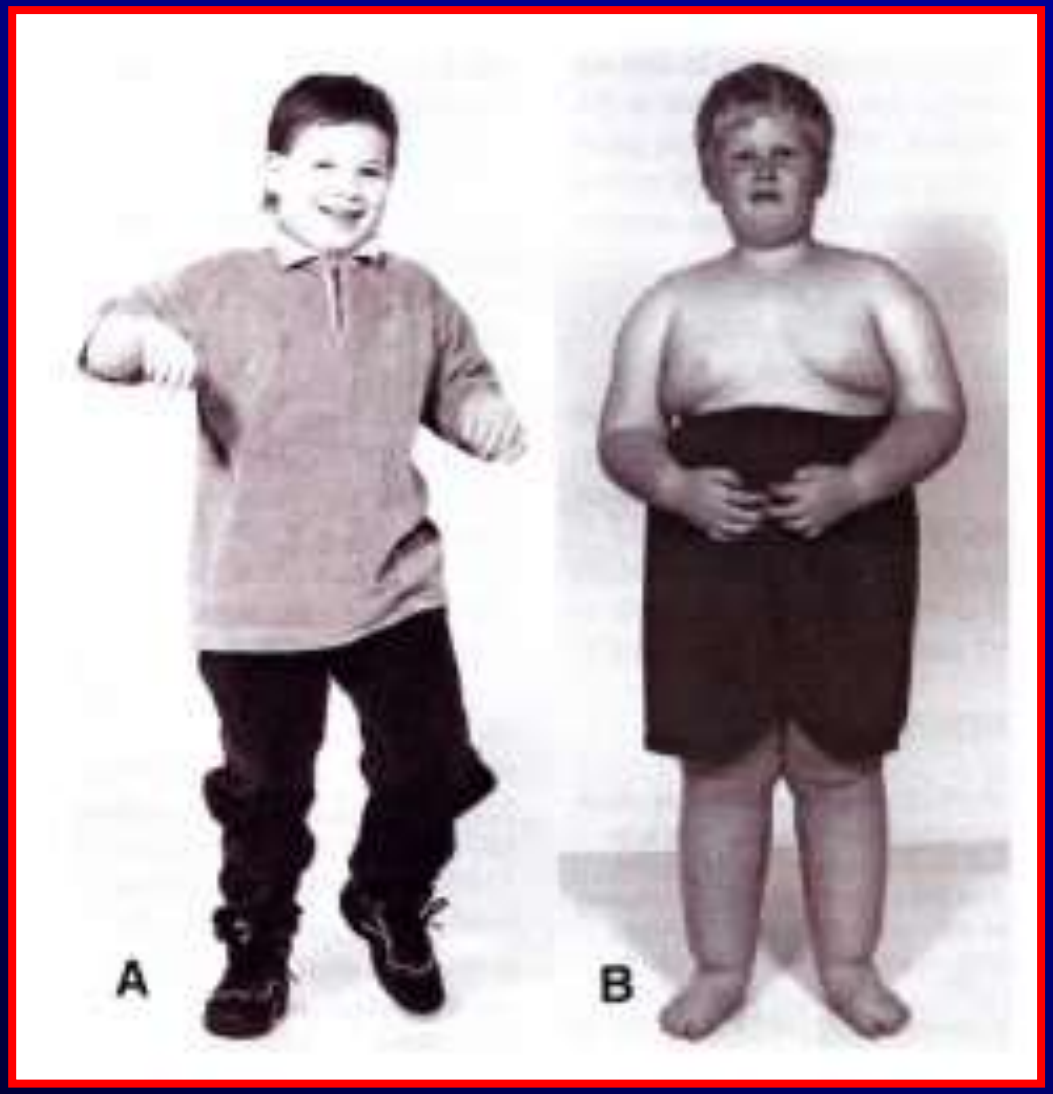
Finally, as **transgenerational inheritance** of **epigenetic alterations** is possible when epigenetic modifications occurs shortly after fertilization. Before specification of the germ line, a complete safety evaluation **might even require studies from a two-generation perspective**

Intrauterine Environment – Genome Interaction and Children's Development: ART and Developmental Disorders

Shiota K. & Yamada Sh.

J. Toxicological Sciences 34:287-291, 2009

Beckwith-Wiedemann syndrome (Courtesy Dr. J.M. Opitz)



Angelman syndrome (A) and Prader-Willi syndrome (B)
(Courtesy Dr. J.M. Opitz)

Conclusions

ART procedures have been associated with the increase in some pre-and perinatal complications in babies. It has recently been shown that ART increase the risk of some imprinting disorders such as BWS and AS in the offsprings and supporting molecular data are being accumulated. The absolute risk may be small, but further investigation is needed to define the risk of ART to cause epigenetic alterations in the zygote

Births Defects in Children Conceived by IVF and ICSI: A Meta –Analysis

Wen J et al.

Fertil. Steril. 97:1331-1337, 2012

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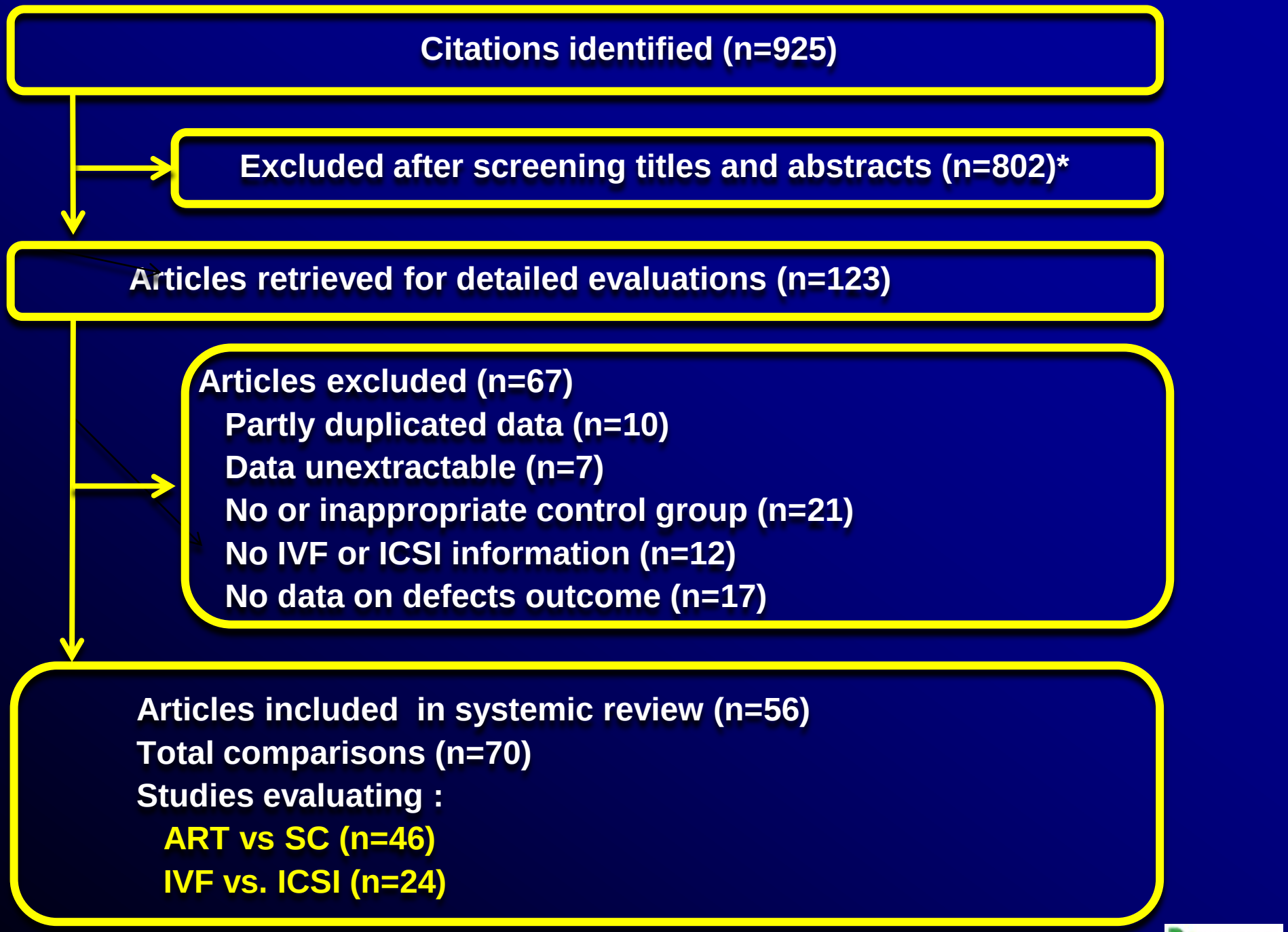
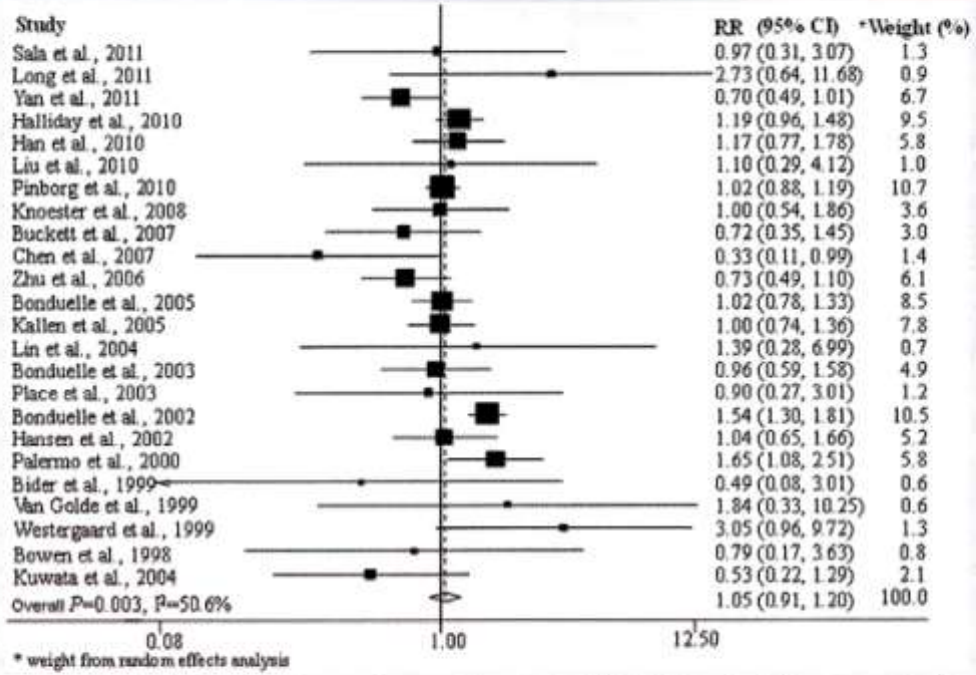

Citations identified (n=925)
Excluded after screening titles and abstracts (n=802)*
Articles retrieved for detailed evaluations (n=123)
Articles excluded (n=67)
Partly duplicated data (n=10)
Data unextractable (n=7)
No or inappropriate control group (n=21)
No IVF or ICSI information (n=12)
No data on defects outcome (n=17)
Articles included in systemic review (n=56)
Total comparisons (n=70)
Studies evaluating :
ART vs SC (n=46)
IVF vs. ICSI (n=24)

FIGURE 3



Individual risk ratio estimates and pooled risk ratio estimates from studies relating birth defects in children conceived by IVF compared with ICSI. Abbreviations as in Fig. 1. *Weight form random effects analysis.

Wen. ART and the risk of birth defects: a meta-analysis. Fertil Steril 2012.

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Conclusions

Factors associated with ART that may increase the risk of **birth defects include the underlying infertility in the couples seeking treatment, and factors associated with the ART procedures themselves.**

Some researchers have argued that the excess risk of birth defects found in infants born after ART treatment may be due to the **underlying infertility of the couples seeking treatment rather than the treatments themselves**

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Conclusions

Taken together, large-scale research on the prevalence of ART-associated birth defects and long-term follow – up of the infants are still essential for the estimation of birth defects risk after ART.

In addition studies of special defects are also needed

Congenital Malformations Associated with Assisted Reproductive Technology: A California Statewide Analysis

Kelley – Quon L. et al

J. Pediatric Surgery 48:1218-1224, 2013

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Materials and Methods

Table 1 Maternal characteristics of ART and FRS groups with matched controls.

	Fertility Related Services			Assisted Reproductive Technology		
	FRS *n = 1,749*	Control *n = 17,476*	*p*	ART *n = 4,795*	Control *n = 46,025*	*p*
Age (y)	33.4 ± 5.4	33.4 ± 5.3	0.877	36.6 ± 5.5	36.1 ± 5.1	**<0.001**
Race:						
White	1,090 (62)	11,069 (63)	0.400	3,272 (68)	30,223 (66)	**<0.001**
Hispanic	326 (19)	3,299 (19)	0.808	590 (12)	7,232 (16)	**<0.001**
Black	50 (3)	430 (3)	0.309	94 (2)	1,176 (2)	**0.012**
Asian	177 (10)	1,756 (10)	0.924	614 (13)	5,466 (12)	0.059
Other	106 (6)	922 (5)	0.164	225 (5)	1,928 (4)	0.100
Parity ≥1	822 (47)	8,210 (47)	0.988	2,603 (54)	24,962 (54)	0.947
Multiples	650 (37)	6,461 (37)	0.873	2,745 (57)	17,603 (38)	**<0.001**

Values are mean ± SD or (%) where appropriate.

Materials and Methods

Table 2 Infant characteristics of ART and FRS groups with matched controls.

	Fertility Related Services			Assisted Reproductive Technology		
	FRS *n = 1,749* *(Singletons: n = 1,099)*	Control *n = 17,476* *(Singletons: n = 11,015)*	*p*	ART *n = 4,795* *(Singletons: n = 2,050)*	Control *n = 46,025* *(Singletons: n = 28,422)*	*p*
Gest. Age (wk)						
All	37.7 ± 3.7	38.1 ± 3.5	**<0.001**	36.9 ± 5.2	38.0 ± 4.0	**<0.001**
Singletons	39.1 ± 2.7	39.4 ± 2.7	**0.002**	38.9 ± 4.0	39.3 ± 3.1	**<0.001**
Preterm Delivery						
All	553 (33)	4,522 (27)	**<0.001**	1,996 (43)	12,423 (28)	**<0.001**
Singletons	132 (12)	886 (8)	**<0.001**	297 (15)	2,663 (10)	**<0.001**
Birth Weight (g)						
All	2,900 ± 820	2,990 ± 750	**<0.001**	2,650 ± 840	2,970 ± 760	**<0.001**
Singletons	3,290 ± 620	3,350 ± 550	**<0.001**	3,240 ± 660	3,340 ± 570	**<0.001**
LBW (<2500 g)						
All	477 (27)	4,175 (24)	**0.002**	1,970 (41)	11,347 (25)	**<0.001**
Singletons	87 (8)	612 (6)	**0.001**	219 (11)	1,722 (6)	**<0.001**
VLBW (<1500 g)						
All	108 (6)	668 (4)	**<0.001**	448 (9)	1,881 (4)	**<0.001**
Singletons	16 (2)	94 (1)	**0.045**	47 (2)	268 (0.9)	**<0.001**
Male Gender						
All	926 (53)	9,246 (53)	0.976	2,456 (51)	23,547 (51)	0.938
Singletons	591 (54)	5,937 (54)	0.938	1,061 (52)	14,463 (51)	0.447

Values are mean ± SD or (%) where appropriate. LBW: Low Birth Weight; VLBW: Very Low Birth Weight.

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Results

Table 3 Unadjusted comparison of major congenital malformations after ART and FRS versus matched controls.

	Fertility Related Services			Assisted Reproductive Technology		
	FRS *n = 1,749*	Control *n = 17,476*	*p*	ART *n = 4,795*	Control *n = 46,025*	*p*
All	119 (9.7)	1,106 (6.3)	0.438	432 (9.0)	3,031 (6.6)	**<0.001**
Neurologic	<10 (<0.6)	84 (0.5)	0.253	30 (0.6)	243 (0.5)	0.379
Eye	<10 (<0.6)	22 (0.1)	0.896	16 (0.3)	75 (0.2)	**0.008**
Head & Neck	17 (1.0)	117 (0.7)	0.147	47 (1.0)	323 (0.7)	**0.031**
Cardiac	55 (3.1)	484 (2.8)	0.365	228 (4.8)	1,357 (3.0)	**<0.001**
Respiratory	<10 (<0.6)	86 (0.5)	0.389	31 (0.7)	223 (0.5)	0.130
Abdomen	12 (0.7)	146 (0.8)	0.510	45 (0.9)	351 (0.8)	0.188
Genitourinary	15 (0.9)	177 (1.0)	0.534	70 (1.5)	457 (1.0)	**0.002**
Limb	17 (1.0)	159 (0.9)	0.795	53 (1.1)	417 (0.9)	0.170
Chromosomal	<10 (<0.6)	58 (0.3)	0.639	<10 (<0.2)	238 (0.5)	**<0.001**
Other	<10 (<0.6)	31 (0.2)	0.956	<10 (<0.2)	108 (0.2)	0.5185

Values are n (%) where appropriate, n < 10 are reported as such by data user agreement.

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Results

Table 4 Adjusted[a] odds of major congenital malformations after ART.

	Overall		Singletons		Multiples	
	OR	95% CI	OR	95% CI	OR	95% CI
All	**1.25**	**1.12–1.39**	1.12	0.93–1.36	**1.35**	**1.18–1.54**
Neurologic	0.98	0.67–1.43	1.09	0.55–2.17	0.99	0.63–1.56
Eye	**1.81**	**1.04–3.16**	1.22	0.43–3.47	**2.41**	**1.28–4.53**
Head & Neck	**1.37**	**1.00–1.86**	1.30	0.82–2.07	1.48	0.98–2.25
Cardiac	**1.41**	**1.22–1.64**	1.16	0.87–1.55	**1.56**	**1.31–1.85**
Respiratory	1.25	0.86–1.82	1.46	0.80–2.67	1.20	0.75–1.93
Abdomen	1.12	0.82–1.54	1.21	0.72–2.03	1.13	0.76–1.67
Genitourinary	**1.40**	**1.09–1.82**	**1.57**	**1.06–2.31**	1.33	0.95–1.86
Limb	1.12	0.84–1.50	1.08	0.67–1.74	1.22	0.84–1.75
Chromosomal	**0.31**	**0.15–0.63**	**0.20**	**0.06–0.70**	0.51	0.23–1.14
Other	0.84	0.43–1.61	0.55	0.16–1.87	1.23	0.56–2.63

[a] Adjusted for maternal age, parity, race, multiple births, infant gender and year of birth.

Conclusions

This report is one of the largest, contemporaneous case-control studies of infants with major congenital malformations born in the U.S after the use of ART and FRS.

Complimentary to the results of prior non-U.S. studies, infants conceived after ART in a region of the U.S. high IVF-ICSI utilization, are demonstrated to have an increased likelihood of birth defects compared to infants conceived naturally even after adjusting for other confounding maternal and infant risk factors

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Conclusions

This demonstrated association may be more pronounced in infants born as **multiples than singletons and may impact the genitourinary, head/neck, eye and cardiac systems more significantly.** Further investigation into the direct causes of these birth defects is paramount to changing the risk profile of infants through the use of ART

Long-Term Follow-Up of Children Concived Through Assisted Reproductive Technology – in China

Lu Y. H. et al

J. of J. Zhejiang Univ.-Sci. 14:359-371, 2013

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Reviewed Topics in China

1. Perinatal Outcome:

- Neonatal Outcome
- Birth Defects

2. Long Term Outcomes:

- Growth and gonadal development
- Physical health
- Neurological and neuro-developmental outcomes
- Psychosocial development
- Risk for cancer

3. Epigenetic abnormalities:

- Imprinted gene defects

Conclusions

Most children conceived by ART are healthy. The main risks for these children are poorer perinatal outcome, birth defects, and epigenetic disorders.
However, whether ART procedures or subfertility itself had led to these changes is still unresolved. Currently, the first IVF-conceived people are now more than 30 years old, and some of them have conceived children

Conclusions

A mouse model study showed that although ART can influence the epigenetic outcome of its offspring, there are no lifelong or transgenerational effects.
However, a mouse study may not allow for meaningful conclusions to be drawn in the human case. **Thus, the health situation for next generation of ART - conceived children is an important question.** In brief, there are still a number of **unanswered questions,** and further, **well-designed studies on the topics described above are urgently needed**

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Impact of ART on Intrauterine Growth and Birth Defects in Singletons

Hansen M. et al

Seminars in Fetal and Neonatal Medicine, 2014

Data from Meta-Analyses

Table 1

Pooled estimates and 95% confidence intervals derived from the meta-analyses of six systematic reviews examining intrauterine growth in ART compared with non-ART singletons.

	Helmerhorst et al. [4]	Jackson et al. [5]	McGovern et al. [8]	McDonald et al. [7]	McDonald et al. [6]	Pandey et al. [9]
Years included in literature search	1985–2002	1978–Oct 2002	1965–2000	1966–Oct 2003	1978–June 2008	1978–2011
No. of studies in meta-analysis of preterm birth[a]	12	14	27	10	15	22
No. of ART infants in meta-analysis of preterm birth[b]	5361	12,114	14,748	3055	<31,032[b]	27,819
Preterm birth (<37 weeks)	2.0 (1.8–2.3)	2.0 (1.7–2.2)	2.0 (1.8–2.2)	1.9 (1.4–2.7)	1.8 (1.5–2.2)	1.5 (1.5–1.6)
Very preterm birth (<32 weeks)	3.3 (2.0–5.3)	3.1 (2.0–4.8)	2.5 (0.9–7.2)	3.0 (1.5–5.8)	2.3 (1.7–3.0)	1.7 (1.5–1.9)
Low birth weight (<2500 g)	1.7 (1.5–1.9)	1.8 (1.4–2.2)	–	1.4 (1.0–1.9)	1.6 (1.3–2.0)	1.6 (1.6–1.8)
Very low birth weight (<1500 g)	3.0 (2.1–4.4)	2.7 (2.3–3.1)	–	3.8 (2.5–5.8)	2.6 (1.8–3.8)	1.9 (1.7–2.2)
Small for gestational age	1.4 (1.2–2.7)	1.6 (1.3–2.0)	–	1.6 (1.2–2.1)	1.4 (1.0–2.0)	1.4 (1.3–1.5)

ART, assisted reproductive technologies.

[a] An indicator of the number of studies included in different meta-analyses. This varies widely depending on the outcome under study. For example, in the Pandey et al. [9]. meta-analysis 22 studies reported on preterm birth and 19 on low birth weight, but only seven reported on small for gestational age.

[b] A rough indicator of the number of ART infants included in different meta-analyses. For the meta-analysis by McDonald et al. [6] it was not possible to determine the exact number of ART infants included in the meta-analysis of preterm birth which included 15 of the 17 studies. The total number of infants in all 17 studies was 31,032.

Data from Meta-Analyses

Table 2

Pooled estimates (95% confidence intervals) derived from the meta-analyses of six systematic reviews examining birth defects in ART compared with non-ART singletons (or singletons and multiples together).[a]

	Rimm et al. [3]	Hansen et al. [2]	McDonald et al. [7]	Pandey et al. [9]	Wen et al. [11]	Hansen et al. [10]
Singletons						
Years included in literature search	1990–Sep 2003	1978–Mar 2003	1966–Oct 2003	1978–2011	1978–Sep 2011	1978–Sep 2012
No. of studies in meta-analysis	IVF: 8 ICSI: 6	15	7	7	–	23
No. of ART infants in meta-analysis	IVF: 2064 ICSI: 3948	13,059	4031	4382	–	48,944
Birth defects	IVF: 1.5 (0.8–2.7) ICSI: 1.3 (0.9–2.0)	1.3 (1.2–1.5)	1.4 (1.1–1.9)	1.7 (1.3–2.1)	–	1.4 (1.3–1.4)
Singletons and multiples together						
No. of studies in meta-analysis	19	25			46	45
No. of ART infants in meta-analysis	35,578	28,638			124,468	92,671
Birth defects	1.3 (1.0–1.7)	1.3 (1.2–1.4)			1.4 (1.3–1.5)	1.3 (1.2–1.4)

ART, assisted reproductive technologies.

[a] Adapted from Hansen et al. [10].

Conclusions

There are still many gaps in our knowledge consequences of current ART practice. Further research is required to examine mechanisms of **epigenetic modification in human embryos, how cryopreservation, including the new cryopreservation techniques, may play a role, and the effect of extended culture on developing embryos.** Using large datasets, it should be possible to start disentangling the inter-related effects of different types of infertility and the multiple aspects of ART treatments

Conclusions

It may also be instructive to examine growth trajectories during pregnancy, rather than relying on gestational age and weight at birth, to improve our understanding of the effects of ART on both poor and excessive intrauterine growth.

These research endeavours, should lead to a **better understanding of the causes of adverse ART outcomes and helps us to identify modifiable risk factors that may further reduce the disparities in outcome between ART and non-ART infants**

Birth Defects and Assisted Reproductive Technologies

Simpson J. L.

Seminars in Fetal and Neonatal Medicine
19:177-182, 2014

Earlier Studies

TABLE 1

Earlier population-based studies of anomalies in assisted reproductive technology pregnancies.

Study	Years of sample accrual	Adjusted OR (95% CI)	Statistical significance	Country
Dhont et al. [4]	1986–2002	1.25 (0.96–1.64)	No	Belgium
Westergaard et al. [3]	1994–1995	1.04 (0.78–1.39)	No	Sweden
Anthony et al. [5]	1995–1996	1.03 (0.86–1.23)	No	Netherlands

OR, odds ratio; CI, confidence interval.

The initial population-based studies depend on data in registries. Ascertainment varied between studies with respect to duration of time in which anomalies were sought and definition of major defects. The interval of accumulated ART registry cases does not in any report correspond to the extant laboratory and ovulation stimulation protocols used in 2014.

Later Studies

TABLE 2

Later population-based studies on anomalies in assisted reproductive technology (ART) pregnancies (2005–2013).

Study	Years of sample accrual	Adjusted OR (95% CI)	Statistical significance	Country
Kallen et al. [6]	1982–2001	1.44 (1.32–1.57)	Yes	Sweden
Davies et al. [13]	1986–2002	1.24 (1.09–1.41)	Yes	Australia (Adelaide)
Halliday et al. [11]	1991–2004	1.36 (1.19–1.55)	Yes	Australia (Parkville)
Hansen et al. [14]	1994–2002	1.53 (1.30–1.79)	Yes	Australia (Perth)
Pinborg et al. [9]	1995–2000	1.24 (0.97–1.58)	No	Denmark
Klemetti et al. [7]	1996–1999	1.31 (1.10–1.57)	Yes	Finland
Ombolet et al. [8]	1997–2003	1.11 (0.08–1.58)	No	Belgium
Kallen et al. [12]	2001–2007	1.25 (1.15–1.37)	Yes	Sweden
Kelley-Quon et al. [15]	2006–2007	1.25 (1.21–1.39)	Yes	USA (California)
Fuji et al. [10]	2006	1.17 (0.81–1.69)	No	Japan

OR, odds ratio; CI, confidence interval.

These population-based studies depend on data in registries. Ascertainment varied with respect to duration of time in which anomalies were sought and definition of major defects. The interval of accumulated ART registry cases does not in any report correspond to the extant laboratory and ovulation stimulation protocols used in 2013.

Reported Meta-Analyses

TABLE 3

Reported meta-analyses on birth defects and assisted reproductive technologies.

Study	Year	Studies accepted	OR (95% CI)
Rimm et al. [16]	2004	19	1.29 (1.01–1.67)
Hansen et al. [17]	2005	25[a]	1.29 (1.21–1.37)
Wen et al. [18]	2012	46	1.37 (1.26–1.48)
Hansen et al. [19]	2013	45[a]	1.32 (1.24–1.42)

OR, odds ratio; CI, confidence interval.

[a] Many studies considered acceptable in the 2005 review by Hansen et al. [17] were no longer considered acceptable in their 2013 report [19].

Conclusions

Assisted reproductive technology is associated with a small (OR:1.3) increase in birth defects. This should be communicated to patients prior to undergoing ART. The counselor may also wish to communicate concern over pitfalls in data used to derive these opinions, but must realize that perfection cannot be achieved in experimental design because the ideal control group cannot be constructed. It is often instructive to remind all couples contemplating pregnancy that the baseline anomaly rate is 2-3%, compared with 3-4% in ART

Conclusions

The consensus to be communicated is that both traditional IVF as well as ICSI/IVF show the same increased risk, except for increased sex chromosome abnormalities and hypospadias in ICSI. Otherwise, no particular organ system seems disproportionately affected. No additive risk seems to exist in ART twins compared with non-ART twins, nor in embryos previously cryopreserved. Overall, **the increased risk observed-irrespective of etiology-seems unlikely to dissuade couples from attempting to have their own children**

Birth Defects and Congenital Health Risks in Children Conceived Through Assisted Reproductive Technology (ART): A Meeting Report

ESHRE Capri Workshop Group

J. Assist. Reprod. Genet.
Published Online 29 May, 2014

Intercellular Interactions

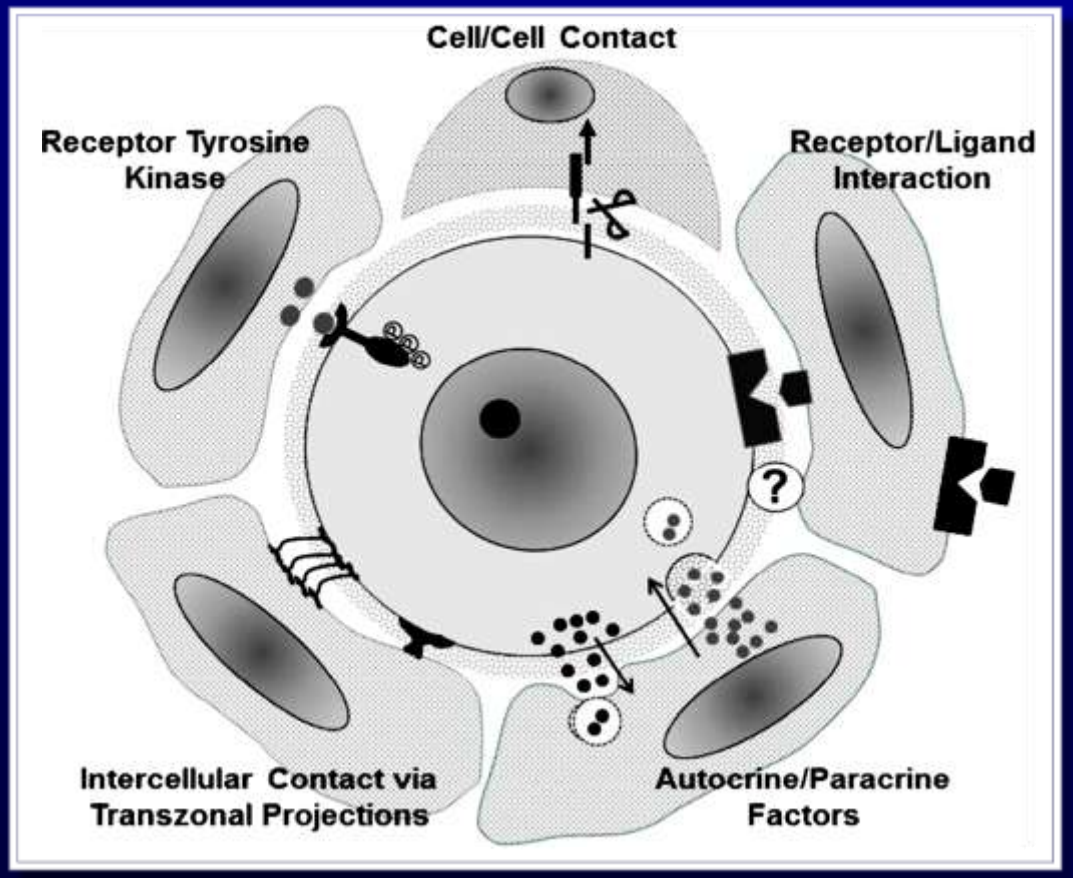

Fig. 1 Currently recognized forms of intercellular interactions between mammalian oocytes and their enveloping granulose cells. Types of signaling interactions depicted are believed to operate at different stages of follicle development to mediate coordination of oogenesis and folliculogenesis and ensure that somatic cells provide metabolic support to the oocyte. Adapted from McGinnis et al. (14)

The Impact of Aging

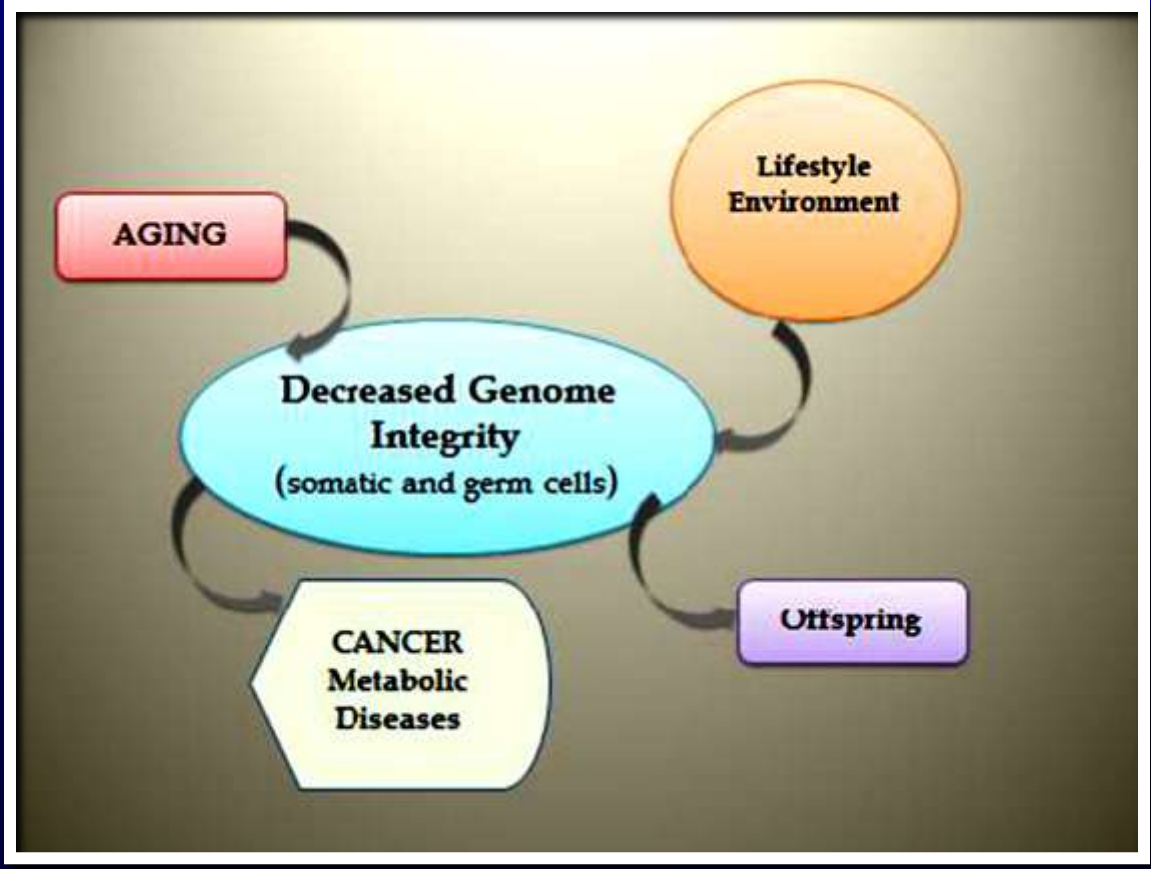

Fig. 2 Schematic depicting impact of aging lifestyle factors (such as diet, smoking) and environmental exposure on the integrity of gonadal germ line and somatic cells. Conditions leading to a loss of genomic integrity are expected to contribute to disease predispositions in offspring.

Human and Bovine Oocytes

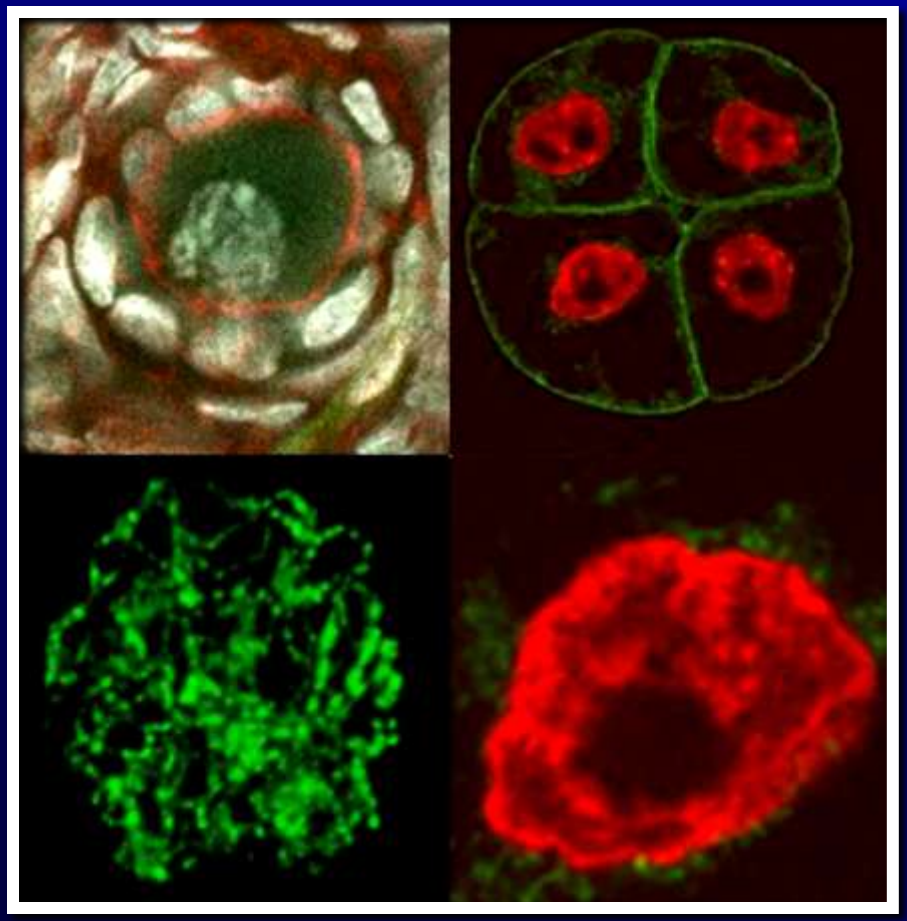

Fig. 3 Chromatin states in human and bovine oocyte nuclei (left) and rat embryo (right) depicting closed (left) or open (right) configurations that in the open state permit ready access of transcription factors ort DNA repair enzymes that would operate less efficiently if chromatin persisted in closed state.

Results

Table 1 Hazard ratios (95 % C.I.) of congenital malformations in singletons conceived either spontaneously or after subfertility treatment according the time to pregnancy [26]

Time to pregnancy (months)	Conceived spontaneously (No. 56.661)	Conceived after treatment for subfertility (No. 4.588)
0-2	1.00	–
3-5	1.16 (1.06 to 1.27)	–
6-12	1.17 (1.06 to 1.30)	1.00
>12	1.29 (1.14 to 1.45)	1.34 (0.94 to 1.92)
Test for trend*	$p<0.0001$	$P=0.10$

*Cox adjusted regression

Nordic Studies

Table 2 Norvegian data on ART conceived children and their siblings

Parameter studied	Total number of singleton deliveries in the reference population	Singleton deliveries after ART	Pairs of singleton siblings *	ART–singletons Adjusted odds ratio, reference population	ART–singletons Adjusted odds ratio compared to sibling born after spontaneous conception
Placenta praevia	882 040**	5,581	1,349	5,6 (4,4–7,0)	2,9 (1,4–6,1)
Delivery <37 weeks	1 127 739***	7,474	2,204	1,69 (1–55–1,85)	1,20 (0,9–1,61)
Small for gestational age	1 1,277 39***	7,474	2,204	1,26 (1,10–1,44)	0,99 (0,62–1,57)
Perinatal death	1 2009 22***	8,229	2,546	1,31 (1,05–1,65)	0,36 (0,2–0,67)

* One singleton from ART, and one from spontaneous conception

[83] *[31]

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Conclusions

Babies born after assisted reproduction differ from neonates born from pregnancies originating from natural conception. They are born earlier, smaller and as a group tend to exhibit a small increase in birth defects.

Assisted reproduction however is here to stay. It allows many previously subfertile and infertile (sterile) couples to have a child (or children) of their own

Conclusions

We should however not close our eyes for the increase in birth defects, especially now that the indications for Assisted Reproduction seem to be getting less and less strict.

The wide divergence in application of IVF related techniques between European countries alone, and the fact that even large scale studies can be published nowadays about women having siblings by both natural and assisted conception, should raise awareness

Risk For Congenital Malformations In Infants Conceived Following In Vitro Fertilization (IVF) Treatment

Lerner-Geva L., Feldberg D. et al

Gertner Institute, Sheba Medical Center,
Sackler School of Medicine, Tel Aviv University,
ISRAEL

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Risk For Congenital Malformations In Infants Conceived Following IVF Treatment

Design	Historical prospective cohort study
Population	**ART group -** all pregnancies in women who underwent ART treatments (IVF & ICSI) in 8 IVF units **Control group -** all pregnancies among women in Clalit Health Services who conceived spontaneously
Period	1997-2004
Methods	The established computerized database of the study cohort was linked to the National Live birth Registry, to determine the results of pregnancy and birth outcome, including the presence of congenital malformations at birth

Congenital Malformations

	All Children		With Malformations		Without Malformations	
	N	%	N	%	N	%
Total	222,330	100	8,113	3.65	214,217	96.35
Group*						
ART	9,042	4.07	541	5.98	8,501	94.02
Control	213,288	95.93	7,572	3.55	205,716	96.45

*P <0.0001

Risk of Congenital Malformations: Multivariate analysis

Group	Number of children	Children with malformations		ART/control	
	N	N	%	OR	95%CI
Control	213,288	7,572	3.55	1.00	
ART	9,042	541	5.98	1.50	1.35-1.66

Adjusted for: Maternal age, sex, treatment year, religion, mother's education, plurality, gestational age

Risk of Congenital Malformations by Plurality

Group		Number of children	Children with malformation		ART/Control	
			N	%	OR*	95%CI
Singleton	Control	202,935	6,993	3.45	1.00	
	ART	4,326	226	5.22	1.55	1.35-1.79
Multiple	Control	10,353	579	5.59	1.00	
	ART	4,716	315	6.68	1.33	1.13-1.55

Adjusted for: Maternal age, sex, treatment year, religion, mother's education, gestational age

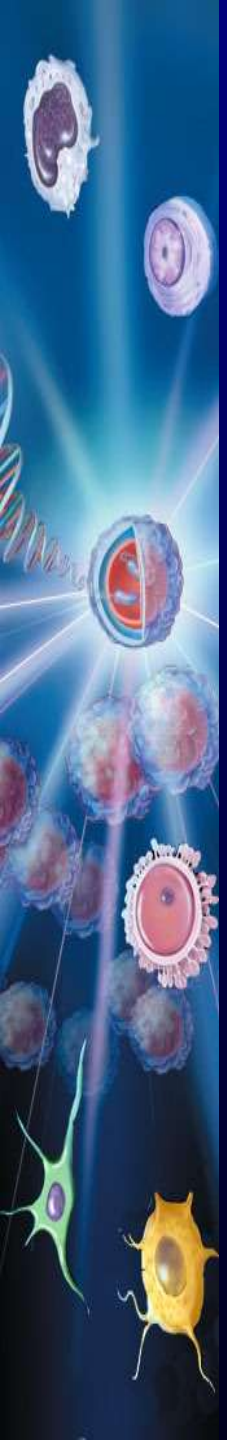
Risk of Congenital Malformations by Plurality & Treatment Type

	Group	Number of children	Children with Malformations		ICSI /IVF	
		N	N	%	OR*	95%CI
All	IVF	3,301	182	5.51	1.00	
	ICSI	5,741	359	6.25	1.12	0.92 - 1.35
Singleton	IVF	1,680	76	4.52	1.00	
	ICSI	2,646	150	5.67	1.33	0.99- 1.78
Multiple	IVF	1,621	106	6.54	1.00	
	ICSI	3,095	209	6.75	0.96	0.74 - 1.24

Adjusted for: Maternal age, sex, treatment year, infertility cause, infertility type

Conclusions

- Children born following ART are at increased risk for congenital malformations
- No differences in risk were observed between IVF & ICSI



Reproductive Technologies and the Risk of Birth Defects

Davies M. et al

N. Eng. J. Med. 366:1803-1813, 2012

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Odds Ratio for Birth Defects According to Type of Assisted Conception and Multiplicity

Type of Assisted Conception	Singelton Births		
	Defect No. of births with defects/ total no. of births	Unadjusted Odds Ratio	Adjusted Odds Ratio
Any	361/4333	1.45 (1.30-1.63)	1.28 (1.14-1.43)
IVF			
Fresh- or frozen - embryo cycles	105/1484	1.25 (1.02-1.52)	1.06 (0.87-1.30)
Fresh - embryo cycles	71/1005	1.25 (0.98-1.59)	1.05 (0.82-1.35)
Fresh - embryo cycles	34/479	1.24 (0.88-1.76)	1.08 (0.76-1.53)
ICSI			
Fresh - or frozen - embryo cycles	91/939	1.72 (1.38-2.15)	1.55 (1.24-1.94)
Fresh - embryo cycles	76/713	1.95 (1.53-2.48)	1.73 (1.35-2.21)
Fresh - embryo cycles	15/226	1.17 (0.70-1.97)	1.10 (0.65-1.85)
GIFT	34/319	1.98 (1.40-2.80)	1.73 (1.21-2.47)
Intrauterine insemination	54/580	1.67 (1.25-2.23)	1.46 (1.09-1.95)
Donor insemination	36/428	1.51 (1.08-2.11)	1.37 (0.98-1.92)
Ovulation induction	19/306	1.08 (0.68-1.74)	0.99 (0.62-1.59)
Clomiphene citrate at home	7/36	3.87 (1.58-9.51)	3.19 (1.32-7.69)
Others	15/241	1.07 (0.63-1.82)	0.96 (0.56-1.63)
Spontaneous conception after previous birth from assisted reproductive technology	96/1306	1.27 (1.02-1.59)	1.26 (1.01-1.57)
Infertile but no history of treatment with assisted reproduction technology	52/600	1.54 (1.15-2.05)	1.37 (1.02-1.83)
No use of assisted reproductive technology and fertile	16.841/293.314	1.00	1.00

Conclusions

Although the large majority of births resulting from assisted conception were free of birth defects, **treatment with assisted reproductive technology was associated with an increased risk of birth defects**, including cerebral palsy, as compared with spontaneous conception. **In the case of ICSI, but not IVF**, the **increased risk** of birth defects **persisted** after **adjustment for maternal age** and several other risk factors

Conclusions

Although we **cannot rule** out the possibility that other **patient factors** contribute to or **explain the observed associations**, our findings can help provide guidance in counseling patients who are **considering treatment for infertility**

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אוניברסיטת בר-אילן

- Main
- Biography
- Publications
- Research
- Awards
- Courses

Professor Benjamin Bartoov

Faculty of Life Sciences

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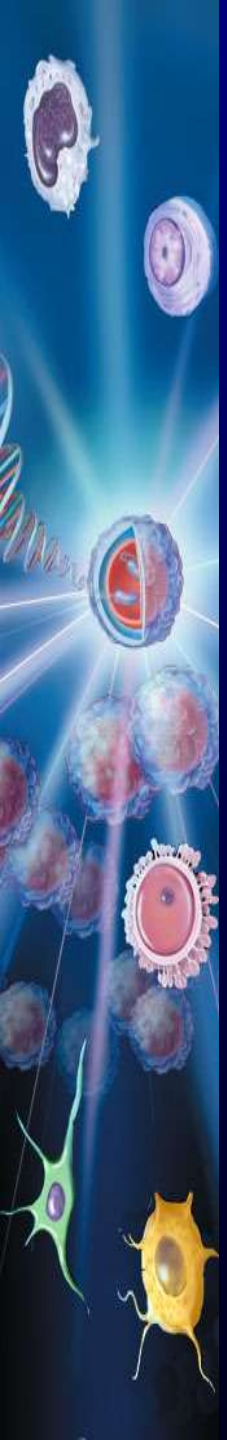
Israel



Selection of Spermatozoa with Normal Nuclei to Improve the Pregnancy Rate with Intracytoplasmic Sperm Injection

Bartoov B. et al

Letter to the Editor; N.E.J.M. 14:1067-1068,2001

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High power ultra-morphology
Motile Sperm Organellar Morphology Examination (MSOME)

1. **High power** inverted light microscopy
2. Fine organellar morphology of **native spermatozoa, real time**, 3D observation
3. **Functional morphology** of only motile sperm cells

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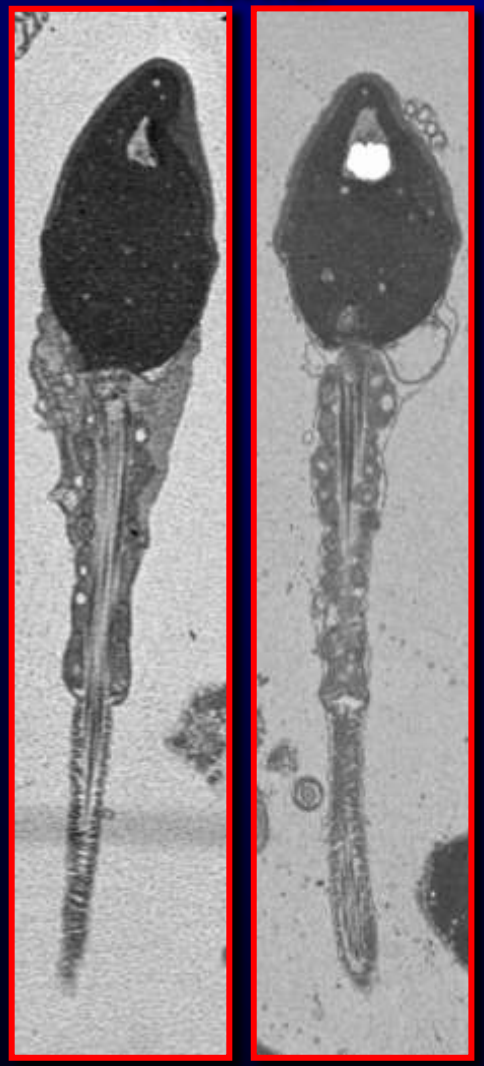
TEM

Fixed
Internal



~20,000 X

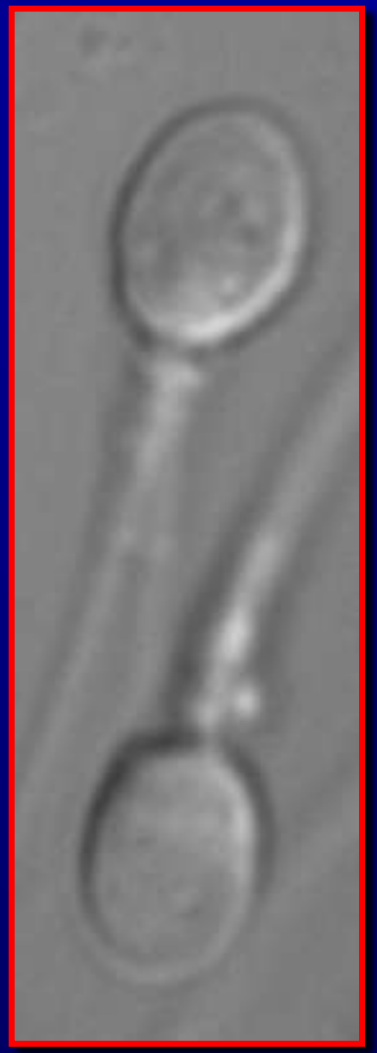
SEM

Fixed
External

~15,000 X

MSOME

Motile
External+internal



~6,000 X

IMSI

1. Definition of correct fine organellar morphology of sperm cells
2. Real time observation of sperm cells by high power light microscopy
3. Examination of the fine organellar morphology of only motile sperm cells
4. Selection of single sperm cells which exhibit correct morphology and using them in IVF-ICSI

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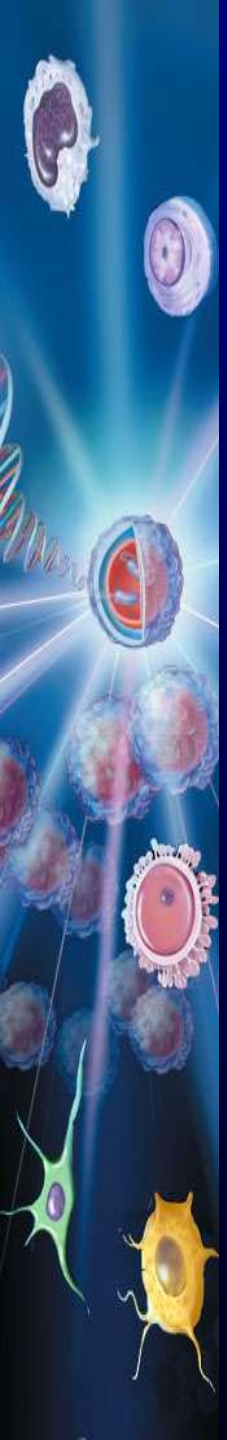

How to Improve IVF-ICSI Outcome by Sperm Selection

Berkovitz A., Feldberg D., Bartoov B.

RBM Online 5: 634-638, 2006

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Implantation Rate

Comparison between	Result
IMSI vs. ICSI (n=80)	31.3±36.3% vs. 9.4±17.4%*
"Best" vs. "Second Best" (n=39)	26.1±26.8% vs. 8.3±15.9%*

* P≤0.01

* P≤0.01

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Pregnancy Rate

Comparison between	Result
IMSI vs. ICSI (n=80)	60.0% vs. 25.0%*
"Best" vs. "Second Best" (n=39)	58.0% vs. 25.7%*
Normal nucleus vs. Vacuolated nucleus (n=28)	50.0% vs. 18.0%*

* P≤0.01

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Early Pregnancy Loss

Comparison between	Result
IMSI vs. ICSI (n=80)	14.0% vs. 40.0%*
"Best" vs. "Second Best" (n=39)	9.8% vs. 33.3%*
Normal nucleus vs. Vacuolated nucleus (n=28)	7.0% vs. 80.0%*

* P≤0.01

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Conclusions

It was confirmed that microinjection by “second best” spermatozoa resulted in significantly lower pregnancy and delivery rates and significantly higher abortion rates than microinjection with “best” spermatozoa.

The present study has strengthened previous conclusions

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IMSI Improves Outcome After ART by Deselecting Physiologically Poor Quality Spermatozoa

Wilding M. & Dale B.

J. Assist. Reprod. Genet.
28:253-262, 2011

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Data for ICSI and IMSI Trial

	Group A (ICSI)	Group B (IMSI)	Significance (P value)
Patients	125	125	1
Cycles started	125	125	1
Mean age (years±SD)	34.2±4.0	33.6±4.5	0.27
Number of oocyte retrievals	110	122	N/A
Number of embryos (% development)	790 (98.9%)	935 (99.4%)	0.43
Number of transferred embryos (Mean±SD)	324 (2.8±1.3)	355 (2.9±1.3)	0.56
Implantation rate (%)	48 (14.8%)	86 (24.2%)	0.003
Number of pregnancies to term	44	79	0.76
Live births	45	84	0.5

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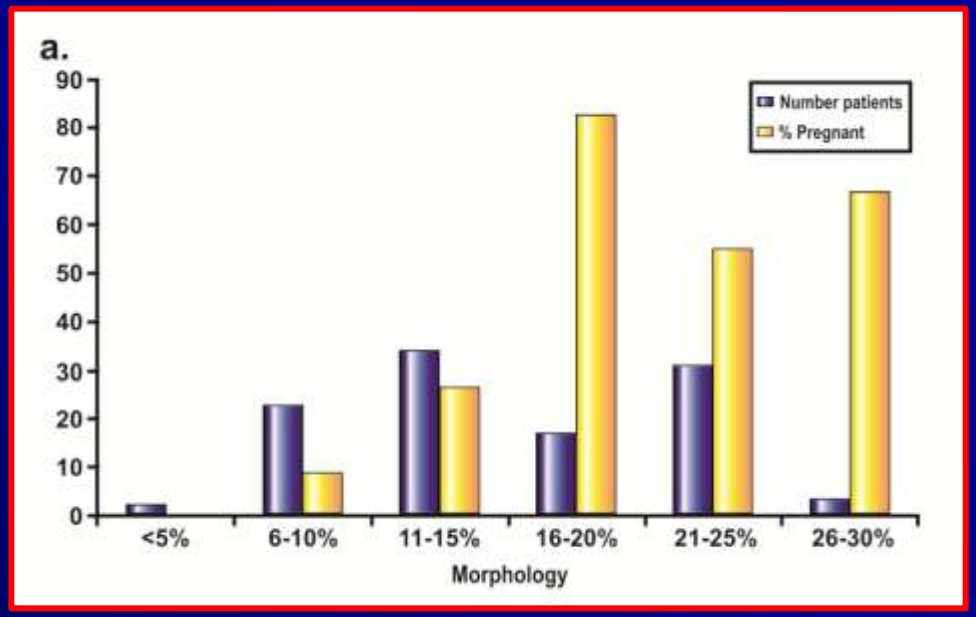
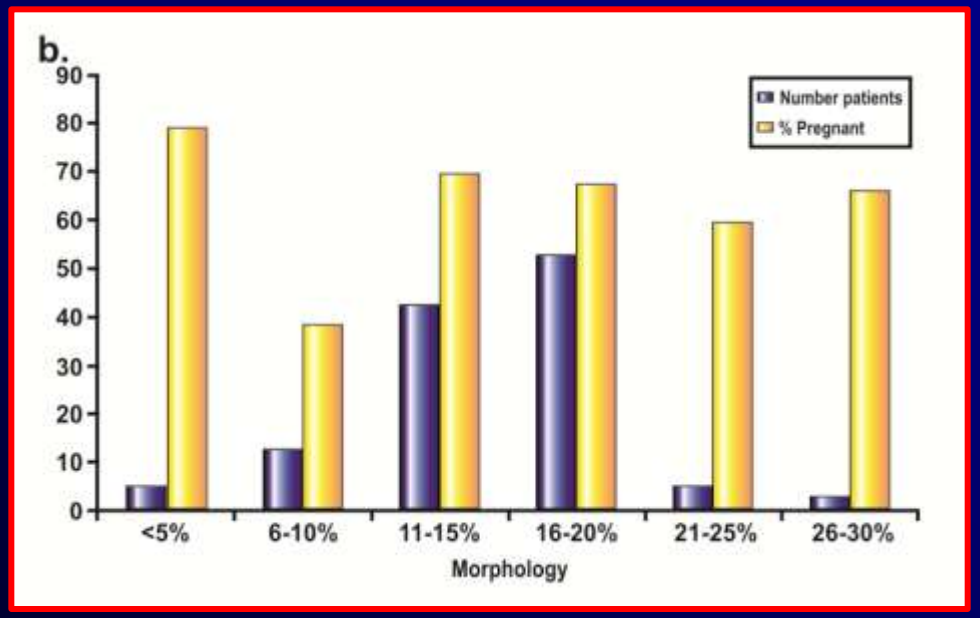


a. ICSI cycles



b. IMSI cycles

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Conclusions

The analysis and selection of spermatozoa for ICSI using **MSOME can improve** results in ART cycles through an increase in the number of **grade A embryos** formed and a **decrease** in the **level of fragmentation** of those embryos. This may occur through a **reduction** in the percentage of abnormal **sperm fragmented DNA**, injected into oocytes

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Summary of IMSI vs. ICSI studies

No consistence in improvement of Early Embryo Development:

- **Fertilization Rate**
- **Percentage of top quality embryos at day two or day three**

Summary of IMSI vs. ICSI studies

A consistant significant improvement in Late Embryo Development:

- **Increased Implantation Rate**
- **Increased Clinical Pregnancy Rate**
- **Increased Live Birth Rate**
- **Reduced abortion rate at the first trimester**

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Organization of chromosomes in spermatozoa: an additional layer of epigenetic information?

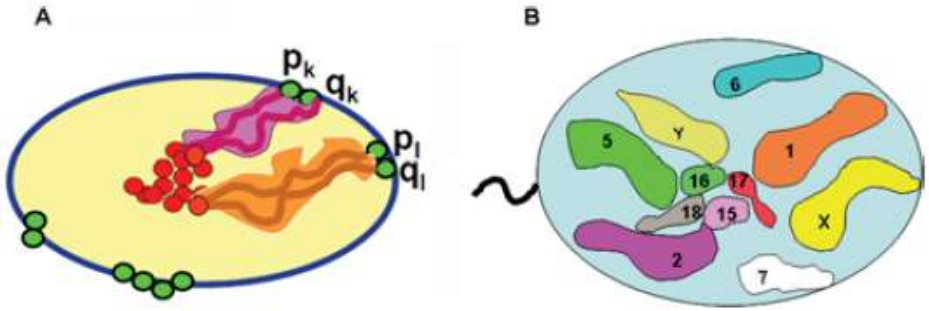
A. Zalensky[1] and I. Zalenskaya
The Jones Institute for Reproductive Medicine, Eastern Virginia Medical School, Norfolk, VA 23518, U.S.A.

Abstract

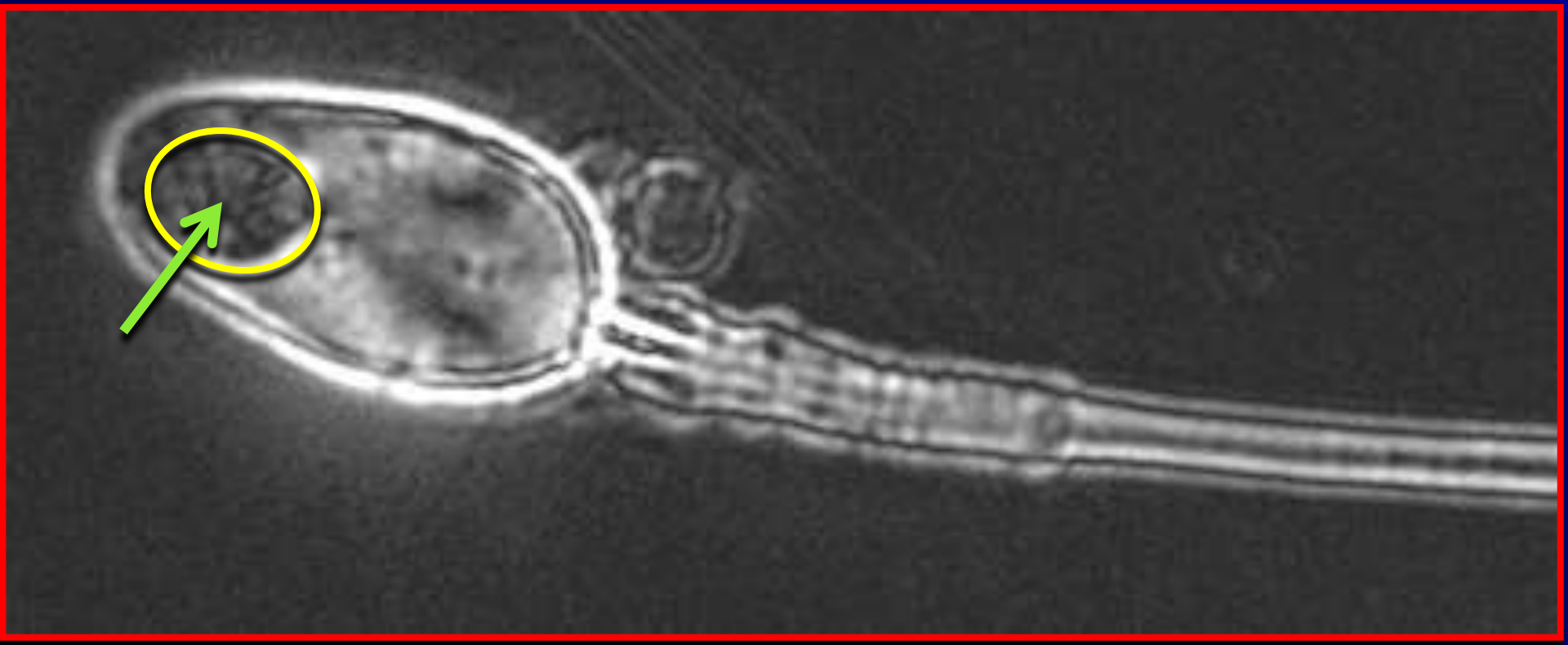
Elaborate non-random organization of human sperm chromosomes at different structural levels, starting from the DNA packing by protamines up to the higher-order chromosome configuration and nuclear positioning of chromosome territories, has been discovered. Here, we put forward a hypothesis that the unique genome architecture in sperm provides a mechanism for orchestrated unpacking and ordered activation of the male genome during fertilization, thus offering an additional level of epigenetic information that will be deciphered in the descendant cells.

Figure 1 | Model of genome architecture (**A**) and intranuclear positioning of chromosomes (**B**) in human sperm

In (**A**), selected chromosome territories, telomeres (green circles) and centromeres (red circles) are shown. (**B**) Schematic representation of the preferred positioning for 11 human chromosomes based on longitude/radial localization and inter-chromosomal distances.



Chromocenter



Interference in the organized chromosomal pattern

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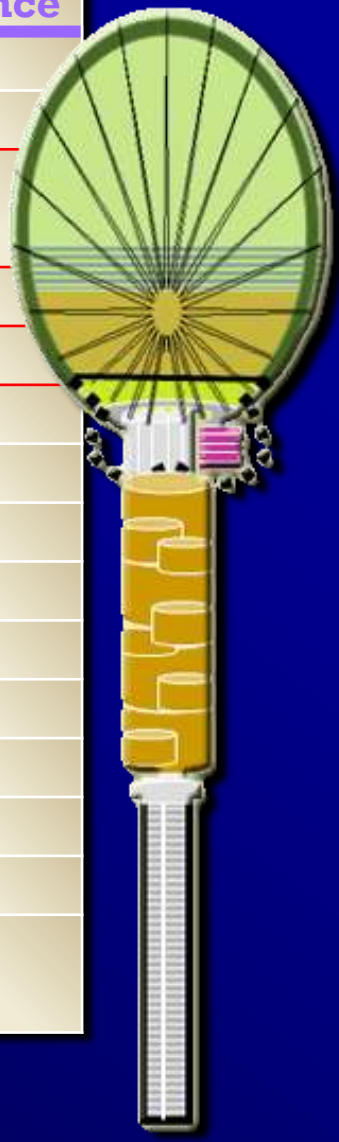
Summary

Organelle	SEM	TEM	Nomarski	Birefringence
Cell membrane	-	+	-	+/-
Nucleus	+	+	+	+
Chromatin organization + Chromocenter	-	-	-	+++
Nuclear membrane	-	+	-	+++
Perinuclear theca	-	-	-	+++
Principal acrosome	+	+	+	-
Equatorial acrosome	+	+	+	-
Post acrosomal lamina	+	++	+	-
Posterior ring	+	++	+	-
Implantation fossa	-	+++	-	+
Capitulum	-	++	-	-
Proximal centriole	-	++	-	-
Mitochondrial sheath	+	++	+	++
Annulus	+	+	+	+
Longitudinal columns + Ribs of fibrous sheath	+	++	-	++



Decreasing Birth Defects in Children by Using High Magnification Selected Spermatozoa Injection (IMSI)

Cassuto N.G. et al

Presented at ASRM Meeting, 2011

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Materials

1028 Neonates

- **578(56%) – ICSI**
- **450(44%) - IMSI**

Magnification x 6100
Cassuto-Barak Classification

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Results

578-ICSI Neonates - 4.15% MCM

450-IMSI Neonates - 1.77% MCM

P<0.03

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Conclusions

Out data shown that IMSI provides significantly less birth defects than ICSI and emphasizes the impact of the sperm head and nuclear morphology defects on congenital malformations of the neonates

IMSI versus ICSI Children - Are they Healthier ?

Berkovitz Arie, Feldberg Dov, Bartoov Benjamin

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Pregnancy Outcome Comparisons Between the IMSI and Matched ICSI Groups

Pregnancy Outcome Parameters	IMSI	ICSI
Analyzed pregnancies (no.)	235	235
Analyzed fetuses (no.)	320	320
Fetuses lost due to a late spontaneous abortion [no. (% of fetuses)]	10 (3.1)	12 (3.8)
Fetuses examined for major congenital malformations (MCM)	310	308
Fetuses eliminated by termination of pregnancy [no. (% of fetuses examined for MCM)]	9 (2.9)	8 (2.6)
Postnatal death [no. (% of fetuses examined for MCM)]	2 (0.6)	2 (0.6)
Live infants [no.(% of fetuses examined for MCM)]	299 (96.4)	298 (96.7)
Live infants with major malformations [no. (% of live infants)]	4 (1.3)	16 (5.2)a
Total fetuses and infants with MCM [no. (% of fetuses examined for MCM)]	13 (4.2)	26 (8.4)b

[a] Comparison between live infants from the IMSI and ICSI groups in the rate of MCM ($p \leq 0.01$)
[b] Comparison between all fetuses/infants from the IMSI and ICSI groups in the rate of MCM ($p \leq 0.01$)

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Question

Is it possible that morphological quality of the spermatozoon injected to the oocyte is a risk factor for major malformation in ICSI treatment?

Answer

Yes it is possible

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Congenital Malformations

Apparently There Are Significantly

Less Congenital Malformations

Among IMSI Children

Take Home Messages

1. The biggest risk for ART are multiple pregnancies

2. Abortion rate is increased by 20-34% compared to spontaneous conceiving

3. This increase is due maternal age, endocrine disorders, PCOD, sub-fertility, ovarian stimulation and invasive procedures as – ICSI, PGD, etc.

Take Home Messages

4. Sex chromosome abnormalities is partially enhanced due to abnormal sperm injection

5. Increase in low birthweight babies three folds

6. Risk for major congenital malformations is increased two folds

Take Home Messages

7. Increased risk for genetic disorders and imprinting of genes with Beckwith-Wiedemann and Angelman's Syndromes

8. The risk of multiple pregnancies can be reduced by Single Embryo Transfer (SET)

9. Lowering the major congenital malformations rate in severe male factor infertility cases, can be performed by high power magnification selected sperm with IMSI procedure

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Thank you