Cancer Risk In Children Born After Assisted Reproductive Technology (ART)

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Introduction

- It is well known that children born after assisted reproductive technology (ART) have more adverse perinatal outcomes
  - **Preterm births**
  - **Low birthweights**
  - **Birth defects**

Introduction

- Currently 1.8% of births occur after ART
- Long term health threats to children conceived after ART
- Cancer is one such adverse health outcome

Question

- Do children and young adults born after assisted reproductive technology (ART) have an increased risk of cancer?

Facts

- Divergent results on cancer risk in children born after ART have been reported in the literature.

Raimondi et al., 2005

- A systematic review and meta-analysis from 2005 including 11 studies showed no overall increased risk of cancer among children born after ART
- (standardized incidence ratio (SIR) 1.33; 95% CI 0.62–2.85)

Hargreave et al., 2013

- Systematic review and meta-analysis indicated a significantly increased risk of all cancers in children born after all kinds of fertility treatment [(relative risk) 1.33; 95% CI 1.08–1.63)].
- Subset of children born after ART, the risk of cancer was increased (RR 1.40; 95% CI 1.12–1.74)
- Significant associations were found for haematological cancers, central nervous system (CNS)/neural tumours and other solid cancers, and for specific cancer types such as leukaemia, neuroblastoma and retinoblastoma.
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Kalen et al. (2010a)

- Large study from Sweden (26 692 children born after ART)
- Significantly increased risk of cancer among children born after ART, compared with children conceived after spontaneous conception (odds ratio (OR) 1.42; 95% CI 1.09–1.87)

Williams et al.,2013

- 106 013 children born in Britain after ART, no increase in the overall risk of cancer was found (SIR 0.98; 95% CI 0.81–1.19).
- In subgroup analyses, increased risks of hepatoblastoma and rhabdomyosarcoma were detected

Table 1 ART and childhood cancer publications discussed in the present editorial

		Children born	Standardized incidence ratio/odds ratio
Wainstock T, et al. Am J Obstet Gynecol (2017)	Singleton	2603 ART children born	1.89 (95% CI 0.89–4.02)
	Infants born population cohort analysis 1991–2013	1721 ovulation induction	2.03 (95% CI 0.96–4.30)
Raimondi S, et al. British Journal of Cancer (2005)	Meta-analysis up to 2005	38,815 ART children	1.33 (95% CI 0.62–2.85) 11 studies
	11 studies—8 excluding three studies with different designs		0.77 (95% CI 0.41–1.42) 8 studies
Reigstad MM, et al. Pediatrics (2016)	Medical Birth Registry of Norway 1984–2011	25,782 ART children born	1.21 (95% CI 0.90–1.63)
Hargreave M, et al. Fertil Steril (2013)	Meta-analysis up to 2011 10 studies	/	1.33 (96% CI 1.08–1.63)
Hargreave M, et al. Int J Cancer (2013)	Danish Infertility Cohort Infertile women 1999–2009	125,844 children born after maternal infertility evaluation	1.18 (95% CI, 1.05–1.32)
Hargreave M, et al. Int J Cancer (2015)	Danish Cancer Registry women 1963–2009	90,888 children born after maternal infertility evaluation	1.18 (95% CI, 1.05–1.32)
Williams CL, et al. N Engl J Med (2013)	UK National Registry of Childhood Tumours 1992–2008	106,013 children born after ART no donor	0.98 (95% CI 0.81–1.19)
Williams CL, et al. Hum Reprod (2018)	Retrospective cohort study 1992–2008	12,137 children born after donor ART	0.83 (95% CI 0.43–1.45)

Fertility drugs

- Risks for acute lymphocytic leukemia and sympathetic nervous system tumors were markedly increased among offspring born to women who used progesterone prior to childbirth.
- Maternal fertility drug use was not associated with overall cancer risk in offspring.

Int. J. Cancer: 136, 1931–1939 (2015) VC 2014 UICC

	Cancer in childhood			Cancer in young adults		
Fertility drug	No. cases	No. in subcohort	HR (95% CI)	No. cases	No. in subcohort	HR (95% CI)
Any						
Never	47	577	1.00	13	366	1.00
Ever	82	712	0.94 (0.60–1.46)	6	217	0.89 (0.36–2.24)
1–2 cycles	41	236	1.26 (0.77–2.07)	2	67	1.01 (0.24–4.33)
≥ 3 cycles	41	476	0.74 (0.44–1.23)	4	150	0.84 (0.28–2.50)
Clomiphene						
Never	90	885	1.00	14	457	1.00
Ever	39	404	0.77 (0.50–1.19)	5	126	1.43 (0.53–3.88)
1–2 cycles	20	145	0.97 (0.57–1.67)	1	49	0.91 (0.12–7.06)
≥ 3 cycles	19	259	0.62 (0.35–1.09)	4	77	1.71 (0.57–5.11)
Gonadotropins[1]						
Never	80	963	1.00	18	563	1.00
Ever	49	326	1.29 (0.71–2.33)	1	20	1.60 (0.24–10.82)
1–2 cycles	30	152	1.57 (0.82–3.03)	0	8	—
≥ 3 cycles	19	174	1.01 (0.51–2.02)	1	12	2.60 (0.43–16.07)
GnRH						
Never	95	1051	1.00	19	583	1.00
Ever	34	238	0.87 (0.49–1.56)	0	0	—
1–2 cycles	21	141	0.89 (0.46–1.70)	0	0	—
≥ 3 cycles	13	97	0.85 (0.42–1.72)	0	0	—
hCG						
Never	67	747	1.00	14	444	1.00
Ever	62	542	0.92 (0.60–1.40)	5	139	1.31 (0.52–3.33)
1–2 cycles	36	225	1.11 (0.68–1.81)	1	47	0.82 (0.13–5.24)
≥ 3 cycles	26	317	0.75 (0.44–1.28)	4	92	1.57 (0.53–4.63)
Progesterone						
Never	91	1067	1.00	19	580	1.00
Ever	38	222	1.46 (0.75–2.85)	0	3	—
1–2 cycles	24	147	1.31 (0.63–2.73)	0	2	—
≥ 3 cycles	14	75	1.91 (0.85–4.29)	0	1	—
Other[2]						
Never	107	1036	1.00	18	501	1.00
Ever	22	253	0.78 (0.48–1.27)	1	82	0.42 (0.06–3.15)
1–2 cycles	15	125	0.91 (0.51–1.62)	1	22	1.12 (0.18–7.22)
≥ 3 cycles	7	128	0.61 (0.28–1.32)	0	60	—

Type of Cancer

- Leukemia
- Lymphoma
- CNS tumor

Sundh et al.

- Cancer in general
- ARTdidn’t increases the risk of childhood cancer (adjusted HR 1.08; 95% CI 0.91–1.27).
- 181 children born after ART (2.0/1000 children) and 638 children born after spontaneous conception (1.8/1000 children) with any form of cancer diagnosis.
- The cancer incidence per 100 000 person-years of observation was 21.0 in children born after ART and 18.8 in children born after spontaneous conception.

Sundh et al

- The mean (+SD) age at diagnosis was 5.6 (4.7) years for children born after ART and 4.9 (4.1) years for children born after spontaneous conception.
- The mortality rate in children with cancer was 14.4% (26/181) in children born after ART, and 10.2% (65/638) in children born after spontaneous conception.
- The mean (+SD) age at death in children with cancer was 5.1 (3.9) years in children born after ART and 5.3 (4.3) years in children born after spontaneous conception.
- No child born after ART had more than one cancer diagnosis.
- Four children in the control group had two recorded diagnoses of cancer.

Table I Children with cancer: maternal and child characteristics by mode of conception.

Characteristics	ART			Spontaneous conception		
	With cancer, *n* = 181	Without cancer, *n* = 91 615	*P*-value[a]	With cancer, *n* = 638	Without cancer, *n* = 357 781	*P*-value[a]
Maternal age at birth (years), median (range)	33.0 (22–44)	33.0 (17–53)	0.50	28.0 (17–42)	28.0 (13–51)	0.75
First birth	125 (69.1)	63 951 (70.0)	0.85	463 (72.7)	249 625 (69.9)	0.14
Later births	56 (30.9)	27 430 (30.0)		174 (27.3)	107 460 (30.1)	
Mode of conception[b]						
Fresh IVF	108 (67.1)	46 060 (63.4)	0.62	NA	NA	
Fresh ICSI[c]	34 (21.1)	18 608 (25.6)		NA	NA	
Frozen	19 (10.5)	8023 (11.0)		NA	NA	
Singletons	109 (60.2)	61 584 (67.2)	0.046	630 (98.7)	350 906 (98.1)	0.31
Twins	71 (39.2)	29 050 (31.7)		7 (1.1)	6419 (1.8)	
Triplets+	1 (0.6)	977 (1.1)		1 (0.2)	456 (0.1)	
Sex, male	95 (52.5)	47 085 (51.4)	0.90	329 (51.6)	183 694 (51.3)	0.85
Gestational age, days, median, range	269 (188–301)	273 (154–309)	0.04	280 (166–304)	280 (154–309)	0.95
<32 weeks	8 (4.5)	3628 (4.0)	0.70	10 (1.6)	3383 (1.0)	0.10
<37 weeks	48 (27.1)	19 355 (21.5)	0.06	55 (8.8)	22 144 (6.3)	0.01
≥42 weeks	8 (4.5)	3776 (4.2)	0.71	59 (9.4)	27 563 (7.8)	0.13
Birthweight, grams, median, range	3140 (795–4820)	3215 (310–5970)	0.11	3523 (530–5705)	3505 (309–5940)	0.36
<1500 g	7 (3.9)	3102 (3.4)	0.68	10 (1.6)	2872 (0.8)	0.04
<2500 g	43 (23.8)	17 049 (18.7)	0.08	44 (6.9)	16 220 (4.6)	0.006
≥4500 g	3 (1.7)	1967 (2.2)	1.0	24 (3.8)	11 076 (3.1)	0.31
SGA[d]	17 (9.6)	6871 (7.7)	0.41	27 (4.3)	11 719 (3.3)	0.20
LGA[d]	6 (3.4)	2237 (2.5)	0.60	32 (5.1)	10 534 (3.0)	0.003
Birth defects, excluding chromosomal aberrations	17 (9.4)	5158 (5.6)	0.04	84 (13.2)	15 624 (4.4)	<0.0001
Chromosomal aberrations	4 (2.2)	212 (0.2)	<0.0001	12 (1.9)	552 (0.2)	<0.0001

Type of Cancer

Table IV Children with first cancer diagnosis (any cancer; types of cancer) by mode of conception.

Cancer diagnosis	ART		Spontaneous conception		All		ART versus spontaneous conception	
	n	Per 1000	*n*	Per 1000	*n*	Per 1000	Crude HR (95% CI)	Adjusted HR (95% CI)[a]
Any cancer diagnosis	181	1.97	638	1.78	819	1.82	1.12 (0.95–1.32)	1.08 (0.91–1.27)
Leukaemias	61	0.66	217	0.61	278	0.62	1.10 (0.83–1.47)	1.06 (0.80–1.41)
Lymphomas	10	0.11	42	0.12	52	0.12	0.94 (0.47–1.88)	0.91 (0.45–1.81)
CNS tumours	42	0.46	114	0.32	156	0.35	1.45 (1.02–2.06)	1.44 (1.01–2.05)
Neuroblastomas and peripheral nerve cell tumours	9	0.10	39	0.11	48	0.11	0.90 (0.44–1.87)	0.87 (0.42–1.80)
Retinoblastomas	4	0.04	31	0.09	35	0.08	0.51 (0.18–1.43)	0.48 (0.17–1.36)
Renal tumours	6	0.07	45	0.13	51	0.11	0.52 (0.22–1.23)	0.51 (0.22–1.19)
Hepatic tumours	4	0.04	6	0.02	10	0.02	2.61 (0.74–9.26)	2.61 (0.74–9.26)
Malignant bone tumours	3	0.03	32	0.09	35	0.08	0.37 (0.11–1.21)	0.35 (0.11–1.15)
Soft tissue/extraosseous sarcomas	9	0.10	28	0.08	37	0.08	1.27 (0.60–2.68)	1.22 (0.58–2.59)
Germ cell tumours	5	0.05	16	0.04	21	0.05	1.23 (0.45–3.37)	1.19 (0.44–3.25)
Other malignant epithelial neoplasms	14	0.15	26	0.07	40	0.09	2.13 (1.11–4.08)	2.03 (1.06–3.89)
Other/not specified malignant neoplasms	14	0.15	42	0.12	56	0.12	1.31 (0.72–2.41)	1.26 (0.69–2.31)

Other studies

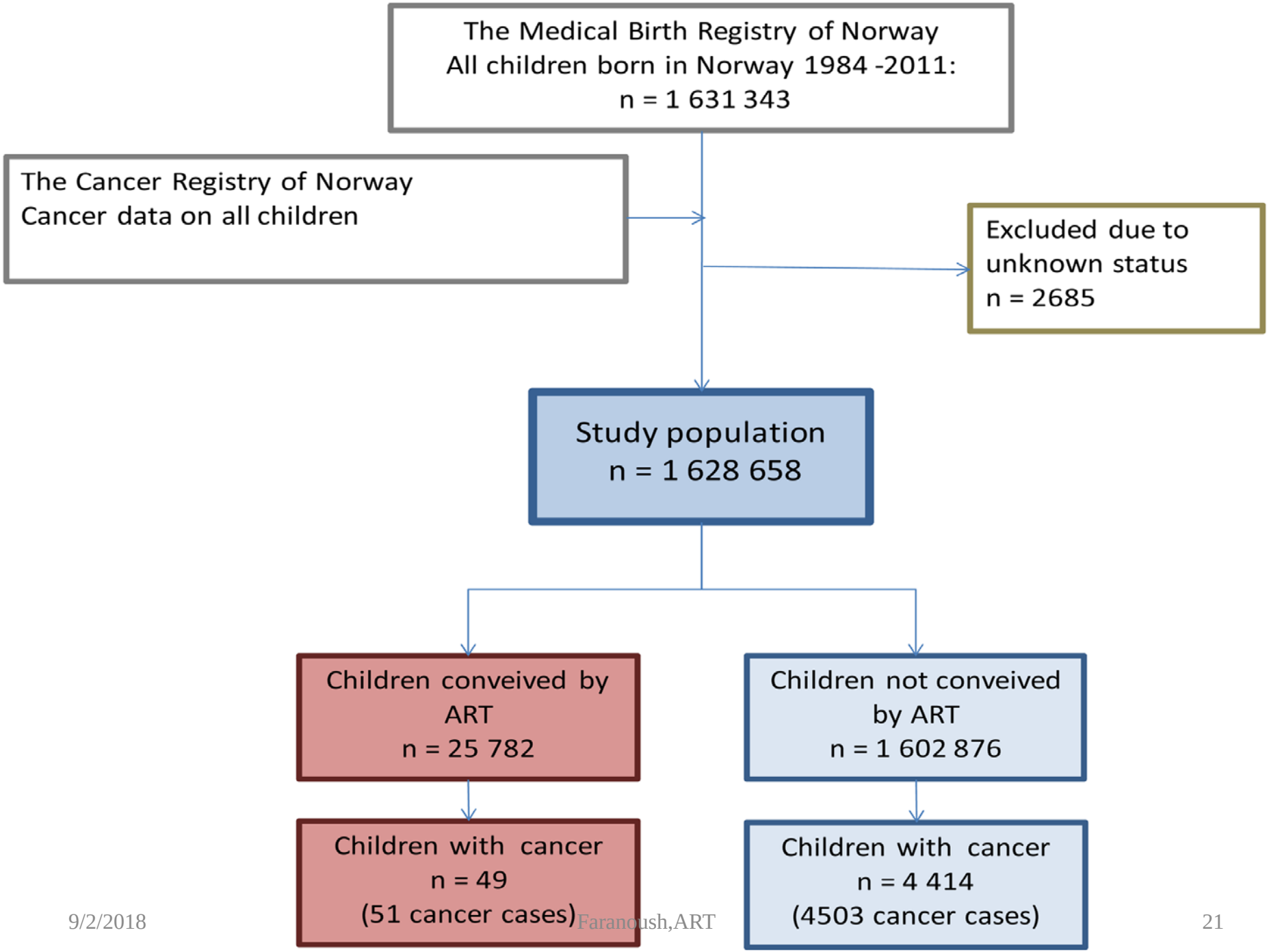
- Increased risk of some types of cancer in children born after ART, e.g. leukaemia, rhabdomyosarcoma and hepatoblastoma, no general pattern has been observed (Petridou et al., 2012,Williams et al., 2013).

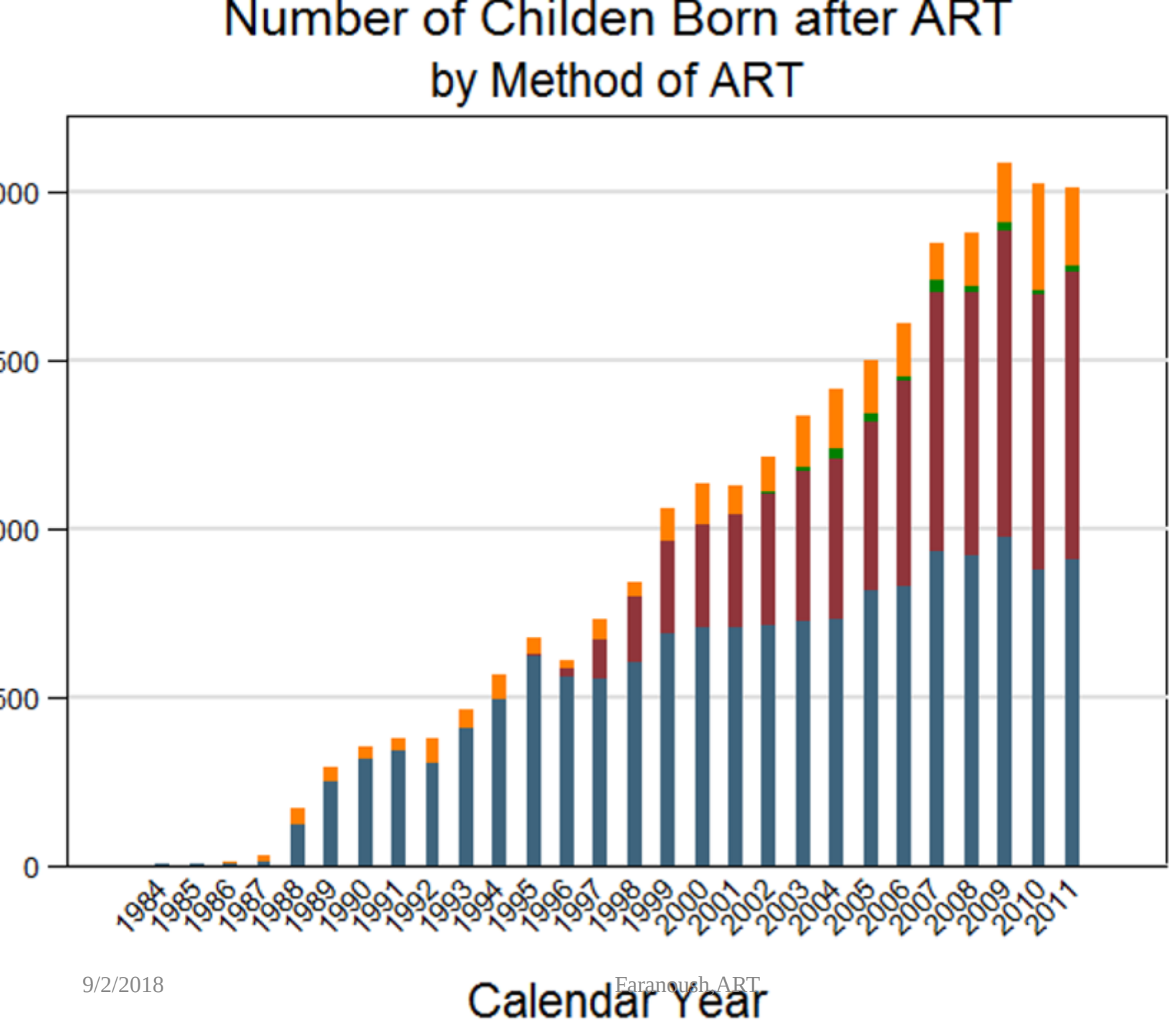
Cont’

- In the systematic review of Hargreave et al. (2013), excluding neural tumours and restricting the analysis to CNS tumours, no significant increase was found in children born after ART.
- Neither in the large UK study, was any increase in CNS tumours found (Williams et al., 2013).

Reigstad et al. 2016

- Cohort 1 628 658 children
- 25 782 were conceived by ART
- Total 4554 cancers, 51 occurred in ART
- Risk of overall cancer was not significantly elevated, HR 1.21 (95% CI 0.90–1.63).
- Increased risk of leukemia was observed for children conceived by ART compared to those who were not, HR 1.67 (95% CI 1.02–2.73).
- Based on small numbers, an elevated risk of Hodgkin lymphoma was found for ART conceived children, HR 3.63 (95% CI 1.12–11.72).


The Medical Birth Registry of Norway
All children born in Norway 1984 -2011:
n = 1 631 343
The Cancer Registry of Norway
Cancer data on all children
Excluded due to unknown status
n = 2685
Study population
n = 1 628 658
Children conveived by ART
n = 25 782
Children not conveived by ART
n = 1 602 876
Children with cancer
n = 49
(51 cancer cases)
Children with cancer
n = 4 414
(4503 cancer cases)


Number of Childen Born after ART
by Method of ART
000
500
000
500
0
Conventional
Fertilisation (
Intracytoplasr
injection (ICS
Other forms
of treatment
Unknown
1984
1985
1986
1987
1988
1989
1990
1991
1992
1993
1994
1995
1996
1997
1998
1999
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
Calendar Year

Risk of cancer in children conceived by ART compared to children conceived without ART, Norway, 1984–2011.

Cancer site	ICCC Site group	Total number of tumors			CRUDE		MODEL II[a]	
		ART	Non-ART	Total	Hazard ratio	95 % CI	Hazard ratio	95 % CI
Leukemia[b]	I	17	1 012	1 029	1.52	0.94—2.45	*1.67	1.02—2.73
Acute lymphatic leukemias	Ia	9	768	777	1.03	0.53—1.98	1.16	0.60—2.27
Acute myeloid leukemias	Ib	5	173	178	*2.65	1.09—6.46	*2.63	1.04—6.64
Other leukemias	Ic–e	3	71	74	*4.91	1.53—15.7	*5.13	1.50—7.60
Lymphoma[c]	II	4	456	460	1.52	0.57—4.08	1.79	0.66—4.90
Hodgkins	IIa	3	258	261	2.62	0.84—8.21	*3.63	1.12—11.72
Non-Hodgkin	IIb	1	147	148	0.93	0.13—6.69	0.99	0.14—7.28
CNS[c]	III	12	1 007	1 019	1.25	0.71—2.21	0.92	0.47—1.79
Astocytomas	IIIb	5	362	368	1.71	0.76—3.83	1.45	0.63—3.29
Embryonal CNS tumors	IIIc	3	175	179	2.13	0.79—5.74	1.70	0.62—4.69
Other gliomas	IIId	1	104	105	1.17	0.16—8.40	1.19	0.16—8.80
Other CNS tumors	IIIf	1	132	133	0.43	0.60—3.06	0.50	0.07—3.59
Neuroblastoma	IV	4	184	188	1.52	0.56—4.08	1.79	0.64—4.99
Retinoblastoma	V	1	90	91	0.75	0.10—5.38	-	-
Renal	VI	3	251	254	1.37	0.44—4.28	1.40	0.44—4.48
Hepatic	VII	2	108	110	2.22	0.54—9.07	1.76	0.41—7.46
Soft Tissue	IX	5	307	312	1.69	0.70—4.09	1.33	0.54—3.30
Others	XI–XII	3	488	491	1.10	0.35—3.44	1.21	0.38—3.82
All		49	4 414	4 463	1.27	0.90—1.63	1.21	0.90—1.63

Genomic imprinting

- Possible association between assisted conception and clinical conditions of genetic origin known as genomic imprinting defects
  - **Beckwith–Wiedemann syndrome (BWS)**
  - **Angelman syndrome (AS**)

Report

Study design

- 1850 new cases referred to MAHAK & Rasool akram Pediatric Cancer Treatment and Research Center
- During 2007 to 2016
- Younger than 15 years old
- Diagnosed with pediatric malignancies

Method

- According to the validated questionnaire
- Evaluating type of pregnancy from parents of patients at the first admission
- Checking the other demographic, diagnosis and treatment of the patients who were positive for ART

ART positive

- Out of 1850 children, 19 patients (1.02%) were born from ART
- This variable had been approved by the parents of the patients

City of born

- These patients had been born in:

- 9 patients from Tehran
- 3 patient from Yazd
- 1 patient from Semnan
- 1 patient from Shahrekord
- 1 patient from Iraq
- 2 patient from Karaj
- 2 patient from Ahwaz

Age of patients

	< 1 year	1-5 years	5 – 10 years	10 – 15 years
Number	4	9	3	3

The age of patients related to the age at the time of diagnosis.

Sex of patients

- 11 patients were male
- 8 patients were female

	< 1 year	1-5 years	5-10 years	10-15 years
Male	2	5	3	1
Female	2	3	2	1

Diagnosis of patients

- 8 children had ALL (B-Cell)
- 5 children had brain tumor
- 4 children had Retinoblastoma
- 1 child neuroblastoma
- 1 child had NHL

Primary disease of patients

- One female child with the age of 12 years old and diagnosis of low grade glioma had primary disease of Neurofibromatosis

Familial marriage of parents

- 6 parents out of 19 reported familial marriage that were cousin (third degree)

Maternal age at birth

< 29	6
30–32	3
33–35	2
>36	8

Birth order of the child

1	11
2	7
>3	2

Last status of the patients

- Two children died during treatment (one male with ALL and one female with LGG)
- 17 children were off treatment and still are under follow-up

Conclusion

- Small increased risk of childhood cancer after assisted conception.
- Larger population based studies are warranted to confirm this and to investigate risk of specific cancers.

Conclusion

- This information is reassuring for couples undergoing ART, the children born after ART and clinicians working with ART.
- The need for continuous follow-up of children born after ART, particularly for uncommon conditions and after newly introduced techniques.


Thank You