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ASSISTED REPRODUCTION TECHNOLOGIES

The risk of birth defects after assisted reproduction

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Abstract
Purpose Aim of this study was to investigate the association between congenital malformations and type of conception (spontaneous or medically assisted).
Methods This is a population based study using data from the regional data base of Lombardy, a Northern Italian Region with a population of about 10 million inhabitants. Included in the study were 277,043 neonates born in Lombardy during the study period 2010-2012. Adjusted and unadjusted odds ratios (OR), and corresponding 95 % confidence intervals (CI), of congenital abnormalities were calculated using unconditional multiple logistic regression.
Results A total of 7057 births (2.5 %) were reported after non spontaneous conception. Overall, the frequency of birth defects was 4.4 % among births after spontaneous conception and 6.7 % among births after non spontaneous ones (OR=1.67, 95%CI=1.5–1.9). The association disappeared after taking into account the confounding effect of maternal age and factors associated with non spontaneous conception. The crude OR of abnormalities was higher than unity for any defect (OR=1.67, 95%CI=1.5–1.9), multiple defects (OR=1.76, 95%CI=1.3–2.3), cardiovascular (OR=2.05, 95%CI=1.8–2.4), musculoskeletal (OR=2.05, 95%CI=1.7–2.5) and metabolic system abnormalities (OR=1.97, 95%CI=1.1–3.5). Almost all these associations, however, disappeared after taking into account potential confounding with the exception of musculoskeletal defects (adjusted OR=1.31, 95%CI=1.1–1.6). In this case also, if adjustment for multiple comparison is taking into account, results did not reach statistical significance.
Conclusions The results of this analysis confirm the recently emerging view that the increased frequency of birth defects observed after ART/medically induced ovulation only is largely due to confounders.

Keywords Birth defect · Congenital malformation · ART · Medically assisted reproduction

Capsule We conducted a population based study, using data from the Lombardy (Northern Italy) regional data base, to investigate the association between congenital malformations and type of conception (spontaneous or medically assisted). The results confirm the recently emerging view that the increased frequency of birth defects observed after ART/medically induced ovulation only is largely due to confounders.

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Introduction

During the last decades several studies have shown an increased risk of birth defects after assisted reproductive techniques (ART). Most recent meta-analyses suggest a 30–40 % increased relative risk [1–3]. Subgroup analyses by organ system suggest that this increase particularly involves genital and cardiac malformations [4, 3], neural tube defects, alimentary atresia, omphalocele and hypospadias among new born infants conceived by in vitro fertilization (IVF) [5, 6].

Part of this association has been attributed to the characteristics of infertile patients. First of all, infertile patients are older than mother of spontaneous conception [7, 4]. Further, it is conceivable that some causes related with infertility may also be linked with the risk of birth defects. For example, infertility is associated with abnormal sperm parameters and in turn men with azospermia or oligospermia have constitutional chromosomal abnormalities that may contribute to the development of birth defects [8, 9]. Along this line, the frequency of birth defects has been shown to be increased among women who conceived spontaneously after a history of infertility [10, 11, 3, 4].

Another topic of discussion is the different potential role of IVF or introcytoplasmatic sperm injection (ICSI) on the risk of birth defects.

A recent pivotal population based cohort study conducted in Australia has confirmed an increased risk of birth defect after assisted reproduction, but it has also suggested that the risk of birth defects associate with IVF, but not after ICSI, was explained by parental factors in multivariate analysis [4]. Overall, the argument remains open and deserves further investigations [3]. Noteworthy, the protocols used for assisted reproduction markedly vary worldwide and is continuously evolving. Furthermore, it has to be pointed out that the vast majority of evidence on the relationship between ART and birth defects were drawn from Northern Europe and Australian studies. This is undoubtedly a scientific pitfall considering that the frequency of birth defect varies worldwide [12] and we cannot exclude that ART may impact differently.

In this paper we analyzed the association between assisted reproduction/medically induced ovulation only and birth defects in Lombardy, Italy, an area of about 10 million inhabitants.

Material and methods

In Lombardy, a standard form is used to register all births and neonatal discharges from public or private hospitals. All admissions and discharges are codified according to the International Classification of Diseases 9th edition—Clinical Modification (ICD-9-CM), Italian version. For all deliveries, information is available for maternal age, maternal country of birth and reason for admission. Neonatal information includes live birth/stillbirth status, sex, congenital abnormalities detected at birth or within the period of hospital admission (mean=4.3 days, SD=7.1, median=3.0, range=1–419). Diagnosis of congenital abnormalities are coded according to the International Classification of Diseases 9th edition—Clinical Modification (ICD-9-CM), Italian version, including structural abnormalities, biochemical abnormalities and those that are chromosomal or otherwise genetic (codes are reported in Table 2). Minor defects are not generally coded and in any case any defect diagnosed after hospital discharge of the neonate is not included. Further at delivery, a specific form is filled by midwifes including information on pregnancy on maternal characteristics type of conception (spontaneous/non spontaneous (i.e., after ART or medically induced ovulation only)), course of pregnancy, delivery and maternal outcome at birth (CedAP data base). This form also includes information regarding neonatal congenital malformation (classified as in the neonatal discharge form, see above). Data from this data base have been linked with the hospital discharge data base in order to obtain detailed information on delivery, pregnancies and maternal and paternal characteristics including type of conception. No information was available on elective terminations of pregnancy for fetal anomaly.

Information on abnormalities was present in both data base. The one of hospital discharge data base was preferred, and used in the analysis, because collected by physician with the aim of obtaining regional reimbursement. This was warranty of quality and completeness. In 288 cases (0.1 %) a birth defect was present in CedAP data base but not in hospital discharge data base. In this case also we considered information contained in hospital discharge data base.

The frequency of birth defects among births after spontaneous or non-spontaneous conception was computed in the total series and separately according to type of ART (IVF and ICSI) or medically induced ovulation only and in strata of selected factors. Chi-square test of heterogeneity was computed to evaluate associations between mode of conception and characteristics of mother and newborn. Odds ratios (OR) and corresponding 95 % confidence intervals (CI) of congenital abnormalities were derived using unconditional multiple logistic regression, fitted by the method of maximum likelihood [13]. Factors included in the model are those statistically associated with the type of conception and are listed in the footnote of the tables.

This is a population based study using data from the regional data base of Lombardy, a Northern Italian Region with a population of about 10 million inhabitants [14].

Results

Table 1 shows the distribution of births after spontaneous and non-spontaneous conception observed in Lombardy during the study period 2010–2012, for a total of 277,043 births according to selected factors.

A total of 7057 births (2.5 %) were reported after ART/medically induced ovulation only. Techniques used were medically induced ovulation only (n=450, 6.4 %) intrauterine insemination (IUI) (n=643, 9.1 %), IVF (n=2194, 31.1 %), ICSI (n=3005, 42.6 %) and others-unspecified (n=765, 10.8 %).

In comparison with women who conceived spontaneously, mother who conceived non spontaneously were older, more educated and more frequently Italian citizen (P<0.001). The father of the child was more frequently older and more educated.

The mean number of ultrasound examinations during pregnancy was 4.7 (SD=2.1) in case of spontaneous conception and 6.3 (SD=2.4) after non spontaneous conception.

Amniocentesis and chorionic villus sampling during pregnancy were more frequently performed after ART/medically induced ovulation only (p<0.0001). However, the difference in amniocentesis frequency was totally explained by the older maternal age at conception after ART/medically induced ovulation only (p-value=0.2630). While, for chorionic villus sampling, the association was statistically significant also after

Table 1 Characteristics of mother and newborns according to mode of conception

	Spontaneous conception (*N*=269,986)*		Non-spontaneous conception (*N*=7057)*		*p*-value***	IVF/ICSI		*p*-value***	IVF		*p*-value***
	N	%**	*N*	%		*N*	%**		*N*	%**	
Maternal age (yrs)											
≤24	28,660	10.7	60	0.9	<0.0001	15	0.3	<0.0001	11	0.5	<0.0001
25–29	58,974	21.9	466	6.6		293	5.7		121	5.5	
30–34	91,841	34.2	1932	27.4		1355	26.1		552	25.2	
35–39	71,969	26.8	2886	41.0		2258	43.5		904	41.3	
40+	17,332	6.5	1700	24.1		1268	24.4		602	27.5	
Mean (SD)	31.8 (5.4)		36.3 (4.8)								
Paternal age (yrs)											
≤29	39,714	15.4	176	2.6	<0.0001	84	1.7	<0.0001	41	2.0	<0.0001
30–34	75,452	29.3	1177	17.4		806	16.2		351	16.8	
35–39	84,796	32.9	2558	37.9		1902	38.2		780	37.2	
40–44	41,460	16.1	1865	27.6		1447	29.1		624	29.8	
45+	16,071	6.2	979	14.5		736	14.8		298	14.2	
Mean (SD)	35.3 (6.0)		39.0 (5.6)								
Maternal education											
University	72,515	27.0	2802	39.8	<0.0001	2120	40.8	<0.0001	786	35.8	<0.0001
High school degree	117,422	43.7	3139	44.5		2306	44.4		1020	46.5	
Primary/intermediate school or no education	78,684	29.3	1108	15.7		770	14.8		388	17.7	
Paternal education											
University	52,240	20.1	2041	30.0	<0.0001	1582	31.5	<0.0001	614	29.1	<0.0001
High school degree	110,415	42.6	3060	44.9		2214	44.1		925	43.9	
Primary/intermediate school or no education	96,835	37.3	1713	25.1		1225	24.4		568	27.0	
Cityzenship of the mother											
Italian	190,834	70.8	6244	88.6	<0.0001	4574	88.1	<0.0001	1895	86.5	<0.0001
Foreign	78,840	29.2	805	11.4		617	11.9		296	13.5	
Geographical area of foreign citizenship											
Europe	25,874	32.8	416	51.7		332	53.8		160	54.0	
Africa	23,476	29.8	157	19.5		116	18.8		61	20.6	
Asia	16,530	21.0	93	11.6		71	11.5		30	10.1	
Southern America	9473	12.0	90	11.2		63	10.2		36	12.2	
USA, Canada	184	0.2	8	1.0		5	0.8		2	0.7	
Other or missing	3303	4.2	41	5.1		30	4.9		7	2.4	
Number of ultrasound examination											
0	4016	1.5	75	1.1	<0.0001	57	1.1	<0.0001	29	1.3	<0.0001
1	3305	1.2	40	0.6		19	0.4		7	0.3	
2	9716	3.6	66	0.9		41	0.8		12	0.6	
3	88,116	32.6	1006	14.3		635	12.2		271	12.4	
4–6	108,839	40.3	2430	34.4		1757	33.8		765	34.9	
7–9	55,994	20.7	3440	48.8		2690	51.7		1110	50.6	
Amniocentesis											
No	234,318	89.0	5621	81.5	<0.0001	4088	80.7	<0.0001	1714	80.0	<0.0001
Yes	28,986	11.0	1273	18.5		979	19.3		429	20.0	
Chorionic villus sampling											
No	246,824	94.0	6164	89.9	<0.0001	4507	89.4	<0.0001	1928	90.4	<0.0001
Yes	15,705	6.0	696	10.1		534	10.6		205	9.6	

Table 1 (continued)

	Spontaneous conception (*N*=269,986)*		Non-spontaneous conception (*N*=7057)*		*p*-value***	IVF/ICSI		*p*-value***	IVF		*p*-value***
	N	%**	*N*	%		*N*	%**		*N*	%**	
Course of pregnancy											
Phisiological	252,253	93.4	5787	82.0	<0.0001	4250	81.9	<0.0001	1792	81.7	<0.0001
Pathological	16,870	6.2	1253	17.8		937	18.1		400	18.3	
Status											
Liveborn	269,528	99.8	7004	99.3	<0.0001	5158	99.5	NE	2177	99.3	NE
Stillborn	117	0.0	17	0.2		13	0.3		7	0.3	
Early neo-natal mortality 0–7 days	190	0.1	21	0.3		8	0.2		6	0.3	
Neo-natal mortality 8–28 days	101	0.0	13	0.2		2	0.03		2	0.1	
Sex											
Male	139,190	51.6	3542	50.2	0.0237	2585	49.7	0.0088	1112	50.7	0.4163
Female	130,796	48.4	3515	49.8		2614	50.3		1082	49.3	
Birth											
Single	263,707	97.7	4721	66.9	<0.0001	3283	63.2	<0.0001	1362	62.1	<0.0001
Twin	6279	2.3	2336	33.1		1916	36.9		832	37.9	
Birthweight (gr)											
<1000	904	0.3	134	1.9	<0.0001	107	2.1	<0.0001	49	2.2	<0.0001
1000–1499	1539	0.6	243	3.4		190	3.7		84	3.8	
1500–2499	15,553	5.8	1695	24.0		1340	25.8		576	26.3	
2500–3999	237,388	87.9	4787	67.8		3433	66.0		1425	65.0	
4000+	14,602	5.4	198	2.8		129	2.5		60	2.7	
Mean (SD)	3240 (518.9)		2819 (716.2)								
Gestational age at birth											
<32	2289	0.9	348	4.9	<0.0001	274	5.3	<0.0001	120	5.5	<0.0001
32–36	16,054	5.9	1688	24.0		1325	25.5		602	27.4	
37–40	210,764	78.2	4420	62.7		3163	60.9		1308	59.6	
41+	40,528	15.0	591	8.4		432	8.3		164	7.5	

NE not evaluable

*In some cases the sum does not add up the total due to missing values

**Column percent

***Heterogeneity Chi–square test

adjustment by maternal age ($p<0.0001$). Considering older mother, both examinations were performed more frequently after spontaneous conception (p-value=0.0151 considering mothers aged 35 years or more for amniocentesis and p-value=0.0001 considering mothers aged 40 years or more for chorionic villus sampling).

A pathological course of pregnancy was more common in women who conceived non spontaneously ($p<0.0001$).

The frequency of multiple births and female births was higher after non spontaneous conception ($p<0.0001$ and $p=0.0237$ respectively) (Table 1).

The mean time at discharge was 4.2 days (SD=6.7, median=3.0, range=1–419) after birth for neonates from spontaneous conception and 8.0 (SD=14.0, median=4.0, range=1–365) after non spontaneous ones.

Overall the frequency of birth defects was 4.4 % among births after spontaneous conception and 6.7 % among births after non spontaneous ones (Table 2). The corresponding OR was 1.67 (95%CI=1.5–1.9). The association disappeared after taking into account the confounding effect of maternal age and factors associated with non spontaneous conception in Tables 1 and 2.

The crude OR of abnormalities was higher than unity for any defect (OR=1.67, 95%CI=1.5–1.9), multiple defects (OR=1.76, 95%CI=1.3–2.3), cardiovascular (OR=2.05, 95%CI=1.8–2.4), musculoskeletal (OR=2.05, 95%CI=1.7–2.5) and metabolic system abnormalities (OR=1.97, 95%CI=1.1–3.5). Almost all these associations however disappeared after taking into account potential confounding with the exception of musculoskeletal defects (adjusted OR=1.31,

Table 2 Abnormalities according to multiplicity

Abnormalities	Singleton births				Multiple births				All births				Unudjusted	Adjusted
	Spontaneous conception		Non spontaneous conception		Spontaneous conception		Non spontaneous conception		Spontaneous conception		Non spontaneous conception			
	N	%	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%	OR (95%CI)	OR (95%CI)
Any defect (any code)	11,440	4.3	264	5.6	524	8.3	208	8.9	11,964	4.4	472	6.7	1.67 (1.5–1.9)	0.95 (0.8–1.1)*
Multiple defects	1487	0.6	35	0.7	60	1.0	27	1.2	1547	0.6	62	0.9	1.76 (1.3–2.3)	1.05 (0.8–1.4)*
Central nervous system (codes 740*–742*)	500	0.2	9	0.2	23	0.4	8	0.3	523	0.2	17	0.2	1.30 (0.7–2.3)	0.78 (0.4–1.4)*
Eye (codes 743*)	57	0.0	3	0.1	1	0.0	–	–	58	0.0	3	0.0	–	–
Ear, face and neck (codes 744*)	258	0.1	6	0.1	1	0.0	2	0.1	259	0.1	8	0.1	–	–
Cardiovascular (codes 745*–747*)	4439	1.7	100	2.1	326	5.2	123	5.3	4765	1.8	223	3.2	2.05 (1.8–2.4)	0.87 (0.7–1.04)**
Respiratory (codes 748*)	140	0.1	3	0.1	10	0.2	–	–	150	0.1	3	0.0	–	–
Grastrointestinal (codes 749*–751*)	960	0.4	24	0.5	24	0.4	11	0.5	984	0.4	35	0.5	1.38 (0.9–2.1)	1.11 (0.7–1.7)**
Urogenital (codes 752*–753*)	2020	0.8	46	1.0	61	1.0	20	0.9	2081	0.8	66	0.9	1.08 (0.8–1.5)	0.91 (0.7–1.3)**
Muscoloskeletal (codes 754*–756*)	2730	1.0	83	1.8	87	1.4	47	2.0	2817	1.0	130	1.8	2.05 (1.7–2.5)	1.31 (1.1–1.6)**¥
Tegument 757*	276	0.1	–	–	5	0.1	1	0.0	281	0.1	1	0.0	–	–
Chromosomal (codes 758*)	382	0.1	6	0.1	5	0.1	2	0.1	387	0.1	8	0.1	–	–
Other non specified (codes 759*)	285	0.1	5	0.1	1	0.0	3	0.1	286	0.1	8	0.1	–	–
Metabolic (codes 24390–27790)	312	0.1	7	0.1	12	0.2	8	0.3	324	0.1	15	0.2	1.97 (1.1–3.5)	1.11 (0.6–2.1)**
Hematologic (codes 282*-286*)	127	0.0	2	0.0	10	0.2	–	–	137	0.1	2	0.0	–	–

Any defect (singleton births); OR=1.39, 95%CI=1.2–1.6

Any defect (multiple births); OR=1.18, 95%CI=0.98–1.4

OR Odds ratio; *CI* Confidence interval

*Adjusted for maternal age, citizenship, maternal and paternal education, parity, fetal sex, course of pregnancy, gestational age, birth-weight, single or multiple delivery (the last one just for the model including all births)

**Adjusted for maternal age, citizenship, parity, fetal sex, course of pregnancy, gestational age, birth-weight, single or multiple delivery (the last one just for the model including all births). The model was calculated excluding cases with missing gestational age

All models were calculated excluding cases with missing categories

¥ Not significant if adjusted for multiple testing

95%CI=1.1–1.6) (Table 2). In this case also, if adjustment for multiple comparison is taking into account, results did not reach statistical significance.

Table 3 shows the odds ratio for any birth defects according to type of non-spontaneous conception and multiplicity. All adjusted odds ratios estimates were not statistically significant.

Discussion

A potential main limitation is the quality of information reported in routine statistics on type of conception and diagnosis of malformation. With regard to the type of conception the frequency of birth after ART reported in the regional data base is largely consistent with the data reported in the Italian Registry of ART [15]. Further, the type of non-spontaneous conception is also consistent with the available data on the clinical practice in Lombardy.

The diagnosis of malformation is based on information available at discharge of the new born. Thus no data are available on malformation that can be diagnosed later in life. With this limitation, the prevalence of malformation reported in the total population is largely consistent with data reported from registry of malformation placed in area included or close to the area considered in this analysis.

Table 3 Odds ratio for any birth defects according to type of assisted conception and multiplicity

Type of assisted conception	Newborns with birth defects		Unudjusted	Adjusted
	N	%	OR (95%CI)	OR (95%CI)*
Spontaneous conception (reference category)	11,964	4.4	–	–
Any type of non spontaneous conception	472	6.7	1.55 (1.4–1.7)	0.95 (0.8–1.1)
Medically induced ovulation only	25	5.6	1.27 (0.8–1.9)	1.15 (0.7–1.8)
IUI	35	5.4	1.24 (0.9–1.7)	0.89 (0.6–1.3)
GIFT	3	5.9	1.35 (0.4–4.3)	1.22 (0.3–5.3)
FIVET	168	7.7	1.79 (1.5–2.1)	1.00 (0.8–1.2)
ICSI	202	6.7	1.55 (1.3–1.8)	0.97 (0.8–1.2)
Other or missing	39	5.5	1.25 (0.9–1.7)	0.69 (0.5–1.0)

All models were calculated excluding cases with missing categories

OR Odds ratio; *CI* Confidence Interval

*Adjusted for maternal age, citizenship, maternal and paternal education, parity, fetal sex, course of pregnancy, gestational age, birth–weight, single or multiple delivery (the last one just for the model including all births)

Further in this study, we observed the well-recognized association between older maternal age and risk of birth defects.

In any case any analysis was conducted in the same data set in comparative terms, thus any misclassification should tend to reduce the observed associations.

Further, it is possible that a higher frequency of birth defects are cause of spontaneous or early induced abortions among fetuses after non spontaneous conception. We have no information from this data set on the number of spontaneous or early induced abortion among pregnancies after spontaneous or non-spontaneous conception. Of particular relevance here is that in our analysis no information on pregnancies terminated because of birth defects before the 180th day of gestation was available. In Italy, terminations of pregnancies before this legal limit are actually considered abortions and no information in these cases are available on the type of conception. This is a potential important limit since it is conceivable that after non spontaneous conception couples may be more closely followed regard the risk of congenital defects. Accordingly, the frequency of invasive procedures is higher among pregnant women after non spontaneous conception (this differences however was totally explained by the older maternal age). Thus, it may be argued that congenital malformations may be more frequently detected among pregnant women after non spontaneous than after spontaneous conception. On the other hand, we observed that the number of ultrasound examinations was higher in pregnancies after non spontaneous conception. The probabilities of diagnosis of late birth defects should consequently be potentially higher in this group. Further, it is possible that a higher frequency of birth defects are cause of spontaneous or early induced abortions among fetuses after non spontaneous conception. We have no information from this data set on the number of spontaneous or early induced abortion among pregnancies after spontaneous or non-spontaneous conception.

In any case this bias should tend to enhance rather than lower the potential association between non spontaneous conception and congenital defect risk.

With regard to potential confounders, we had the opportunity of taking into account the effect of maternal and paternal age and education. Unfortunately we have no information on time to conception in couples who conceived spontaneously.

Among the strengths of this study we should considered the population based design and the large sample size. Moreover, to our knowledge, this is the first contribution from Southern Europe and refers to a recent historical period (2010–2012).

The general results of this study confirm previous findings of an increased frequency of birth defects among babies born after ART [1–3]. The risk, however, disappeared after taking into account in the analysis the effect of maternal age, parity, citizenship, education and multiple pregnancies. In our analysis also no differences emerged between FIVET-ICSI and other procedures. This finding is not totally consistent with previous data. It has been indeed suggested, although not consistently, that ICSI procedure may increase the risk of birth defects [7, 16]. In a large analysis from Australia that has included information from 139 defects after ICSI, the risk of birth defects after ICSI was 1.57 (95%CI: 1.30–1.90) after taking into account potential confounding factors. It has also been suggested that this effect is biologically plausible. On the other hand, as previously alluded, characteristics of

couples which undergo ICSI may be different from those treated with FIVET [4]. Along this alternative view, in our population no differences emerged between women treated with ICSI and FIVET according to factors considered in Table 1.

In the previous quoted Australian study an increased risk of congenital malformations was observed after induction of ovulation at home with clomiphene citrate and intrauterine insemination [4]. Similar results emerged from case-control studies [4]. Lacking of a clear biological explanation of these findings, caution should be considered in the interpretation of these results.

Subgroup analyses documented an increased risk for musculoskeletal abnormalities in our study. This finding is surprising. Noteworthy, based on previous literature, a possible concern emerging from previous organ system analyses relates to hypospadias and cardiac defects [4, 3]. Considering this evidence, the absence of any biological rational for identifying an isolated increased risk in musculoskeletal abnormalities and the absence of a statistically significant associations when considering all birth defects together, we concluded for a type 1 error.

Even if some initial studies suggested that the risk of congenital malformation after IVF-ICSI is higher in twins compared to spontaneous twin pregnancies, this has not been subsequently confirmed [17, 2]. A confounder here is that birth defects are increased per se in twin pregnancies, in particular if monozygotic [4, 2]. Adjusting for multiple pregnancies is thus crucial. No differences in the frequency of birth defects between spontaneous and ART related twins emerged from our analysis.

In conclusion the results of this analysis confirm the recently emerging view that the increased frequency of birth defects observed after ART/medically induced ovulation is largely due to confounders.

References

1. Wen J, Jiang J, Ding C, Dai J, Liu Y, Xia Y et al. Birth defects in children conceived by in vitro fertilization and intracytoplasmic sperm injection: a meta-analysis. Fertil Steril. 2012;97(6):1331–7e1-4. doi:10.1016/j.fertnstert.2012.02.053.
2. Hansen M, Kurinczuk JJ, Milne E, de Klerk N, Bower C. Assisted reproductive technology and birth defects: a systematic review and meta-analysis. Hum Reprod Update. 2013;19(4):330–53. doi:10.1093/humupd/dmt006.
3. Simpson JL. Birth defects and assisted reproductive technologies. Semin Fetal Neonatal Med. 2014;19(3):177–82. doi:10.1016/j.siny.2014.01.001.
4. Davies MJ, Moore VM, Willson KJ, Van Essen P, Priest K, Scott H, et al. Reproductive technologies and the risk of birth defects. N Engl J Med. 2012;366(19):1803–13. doi:10.1056/NEJMoa1008095.
5. Van den Bergh M, Emiliani S, Biramane J, Vannin AS, Englert Y. Impact of the introduction of intracytoplasmic sperm injection (ICSI) on the treatment of severe male sterility. Rev Med Brux. 1999;20(5):A453–6.
6. Ericson A, Kallen B. Congenital malformations in infants born after IVF: a population-based study. Hum Reprod. 2001;16(3):504–9.
7. Isaksson R, Gissler M, Tiitinen A. Obstetric outcome among women with unexplained infertility after IVF: a matched case–control study. Hum Reprod. 2002;17(7):1755–61.
8. Harper JC, Geraedts J, Borry P, Cornel MC, Dondorp W, Gianaroli L, et al. Current issues in medically assisted reproduction and genetics in Europe: research, clinical practice, ethics, legal issues and policy.European Society of Human Genetics and European Society of Human Reproduction and Embryology. Eur J Hum Genet. 2013;21 Suppl 2:S1–S21. doi:10.1038/ejhg.2013.219.
9. http://sogc.org/ The Society of Obstetricians and Gynaecologists of Canada. Last Accessed on 19 May 2014.
10. Jaques AM, Amor DJ, Baker HW, Healy DL, Ukoumunne OC, Breheny S, et al. Adverse obstetric and perinatal outcomes in subfertile women conceiving without assisted reproductive technologies. Fertil Steril. 2010;94(7):2674–9. doi:10.1016/j.fertnstert.2010.02.043.
11. Rimm AA, Katayama AC, Katayama KP. A meta-analysis of the impact of IVF and ICSI on major malformations after adjusting for the effect of subfertility. J Assist Reprod Genet. 2011;28(8):699–705. doi:10.1007/s10815-011-9583-z.
12. http://www.eurocat-network.eu/ European Surveillance of Congenital Anomalies. Last Accessed on 19 May 2014.
13. Breslow NE, Day NE (1980) Statistical methods in cancer research. Vol. I. The analysis of case–control studies. IARC Scientific Publications No. 32. Lyon.
14. http://www.istat.it/it/ Istituto Nazionale di Statistica (Italy). Last Accessed on 19 May 2014.
15. Italian Registry of ART. http://www.iss.it/rpma/ Last Accessed 27 Jun 2014.
16. Kurinczuk JJ, Bower C. Birth defects in infants conceived by intracytoplasmic sperm injection: an alternative interpretation. BMJ. 1997;315(7118):1260–5. discussion 5–6.
17. Helmerhorst FM, Perquin DA, Donker D, Keirse MJ. Perinatal outcome of singletons and twins after assisted conception: a systematic review of controlled studies. BMJ. 2004;328(7434):261. doi:10.1136/bmj.37957.560278.EE.