Journal of Assisted Reproduction and Genetics (2018) 35:1773–1775
https://doi.org/10.1007/s10815-018-1274-6

EDITORIAL

Assisted reproductive technologies (ART) and childhood cancer: is the risk real?

Paolo Emanuele Levi-Setti[1] · Pasquale Patrizio[1,2]

Received: 19 May 2018 / Accepted: 17 July 2018 / Published online: 24 July 2018

Recently, the report of an increased risk of childhood cancers after assisted reproductive techniques (in vitro fertilization/intracytoplasmic sperm injection (IVF/ICSI)) has generated considerable concerns [1]. However, is this accurate information? In recent years, in Italy and in parts of America of the restoration creationism [2], particularly when the issues involve contraception, hormonal therapies, and assisted reproduction techniques, debates generated by false or incorrect news are increasing. In fact, many of the associations between risk factors and diseases published by observational clinical research are often inaccurate, while the weight of a correlation is often exaggerated. This problem has many causes, including the inability of authors, reviewers, and editors (even of highly prestigious journals), to recognize the inherent limitations of these studies.

This is particularly true for associations, defined as relative risks (RR) or odds ratios (OR), less than 4 times the probability that the event will occur in the absence of the condition under investigation. Such relationships are often attributed to bias or mere randomness rather than to a real cause-effect relationship. In general, only cohort studies with RR greater than 2 or 3 and case-control studies with OR higher than 3 or 4 (or 2–4 times the incidence in the control population) should be regarded as credible.

A recent example of inaccurate reporting is the Israeli study cited by many newspapers [1] that presented retrospective data on 242,187 children of which 2603 (1.1%) born through IVF, 1172 (0.7%) conceived with help of medications to induce ovulation but not IVF, and 237,863 (98.3%) conceived naturally. The first important observation is that the ages of the mothers in the three groups (IVF, use of fertility drugs and natural) were different. Furthermore, there were differences in number of pregnancies and gestational age, premature birth, delivery and birth weights, hypertension, pre-gestational diabetes, gestational diabetes, and pregnancy-induced hypertension among the groups. In the study period (0–18 years), 429 children (1.77%) were hospitalized with a diagnosis of malignancy, including 7/2603 = 0.26% from IVF, 7/1172 = 0.59% from the use of fertility drugs, and 415/237,863 = 0.174% from natural conceptions.

Multivariate analysis, without considering many other confounding factors, showed a relative risk of 1.89 (OR 0.894.02) after IVF and 2.03 (OR 0.96–4.30) after ovulation induction, when compared to natural conceptions. The incidence of a malignancy was low in children conceived spontaneously and after IVF, although for some specific malignancies like acute lymphocytic leukemia (ALL), due to the presence of genetic mutations, there was an increase [3]. The authors concluded that it was difficult to determine if the adverse events were related to fertility treatments or to the condition of being infertile [2].

After extensive discussions and review of the current literature on the topic of ART and risk of childhood cancer (articles discussed are listed in Table 1), we decided to write this commentary to highlight what is known and unknown on this important topic. The main biological question is whether IVF and embryo development from the 2 to 150 cells (about 2 to 5 days) in the laboratory cause an increased risk for cancers in childhood and adolescence. The theme is extremely relevant, as one couple in six has reproductive difficulties or a diagnosis of infertility and between 1 and 8% of annual births in some countries are from ART [4, 5].

A meta-analysis published in 2005 [6] reported on 11 of 14 published data sets, containing pertinent, non-overlapping, and comparable data. The final cohort included 38,815 subjects, with 38.21 cases of cancer expected vs 47 observed, giving a standardized incidence ratio (SIR) of 1.23 (95% CI 0.93–1.37). The analysis restricted to eight studies indicated 36.22 expected cases of childhood cancer and 35 observed, giving an SIR of 0.97 (95% CI 0.69–1.10).

✉ Paolo Emanuele Levi-Setti
paolo.levi_setti@humanitas.it

[1] Humanitas Fertility Center, Rozzano, Milan, Italy

[2] Yale Fertility Center, New Haven, CT 06511, USA

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)

In 2016, the Norwegian Register of births published a cohort study on all births occurred between 1984 and 2011 linking them with the Norwegian cancer registry data. In total 1,862,876 children were conceived spontaneously and 25,782 after ART. In spontaneous conceptions, there were 4523 cancer cases (4523/1,862,876 = 0.24%) and 49 in ART-conceived offspring (49/25,782 = 0.19%). No correlation was found between cancer and ART (HR 95% CI 0.90, 1.63–1.21) and although the authors found an increase in certain types of leukemia and lymphoma, they concluded that the power of their study and numbers of cancers found was too small to give a real estimation [7].

A 2013 meta-analysis (including ten studies) [8] indicated an increase in relative risk for children born after IVF of childhood tumors (RR 1.33; OR, 1.08–1.63), but the same authors published two cohort studies on 2,830,054 children born in Denmark between 1964 and 2006 and 1999 and 2006. In total, 125,844 and 90,888 children respectively were born from mothers diagnosed with infertility, a condition that needs be accounted for a possible cause-effect on the risk of cancer [9, 10].

The analysis was carried out separately for childhood cancers (0–18 years) and young adults (> 20 years). Children born to women with infertility problems showed an increased risk for all types of cancer, both in childhood (1.18; CI, 1.05–1.32) with significantly increased risk of leukemia (1.30; CI, 1.06–1.60) and as young adults (1.22; CI, 1.04–1.43) for endocrine tumors (2.67; CI, 1.35–5.29). If confirmed, this would lead to an increase, small but important, of four malignancies in childhood and about nine in young adults for every 100.000 born after exposure to infertility prior to conception.

Very recently, Williams et al. [11] reported on 106,013 children born in Britain between 1992 and 2008 after assisted conception without donor involvement with data from the UK National Registry of Childhood Tumours to determine the number of children who developed cancer before 15 years of age. One hundred eight cancers were identified after assisted conception vs the 109.7 expected (standardized incidence ratio, 0.98; 95% confidence interval [CI], 0.81 to 1.19; $P = 0.87$). There was no increase in the overall risk of cancer among children born after assisted conception during the 17-year study period. An increased risk of hepatoblastoma and rhabdomyosarcoma was detected, but the absolute risk was mall.

Another recent study [12] reported data on all children born in Britain from 1992 to 2008, cross referencing with 12,137 children born from gametes (oocyte and sperm) or embryo donation and followed up until 15 years of age with data from the cancer registry. Overall, 12 cancers were observed, and this figure was lower than the expected, 14.4 (standardized incidence ratio 95% CI 0.43–0.83; 1.45; $P = 0.50$). This result is extremely important, reporting a reduced risk when IVF utilizes gametes of young donors. A small increased risk was observed only for hepatoblastoma, but the numbers and absolute risks were too small (5 cases; SIR 10.28; 95% CI

1.25–37.14; *P* 0.05) for a correct risk analysis and this tumor was associated with low birth weight, as discussed by the authors [11, 12].

An important consideration deserving further studies is the topic of an increasing number of women (and men) approaching maternity and parenthood at older ages. This socio-demographic phenomenon exposes couples to an increased risk of not conceiving or to a prolonged time to conceive [13–15]. In addition, children of older parents [16, 17] have an added increased risk, although modest in terms of numbers, of developing metabolic diseases, diabetes, neurological anomalies, and tumors. Therefore, while a pregnancy after age 40 can still have a beneficial effect for the mother [18] and there exists a relationship between fertility and longevity [19, 20], future studies assessing the risk of infertility and cancer must take into account age, genetic, epigenetic, and environmental confounding factors.

In conclusion, there is no increased risk of cancer in childhood and young adults conceived with IVF. Likewise, the risk of birth defects [21, 22] and cancer in women who use fertility drugs is not increased when compared to homogeneous populations by age, risk factors, and controlled for the condition of infertility [23].

As a final point, to better capture meaningful data, both national and international registry reporting outcomes after ART should be cross linked with cancer registries. A specific set of variables associated with increased risk for cancer such as type and duration of infertility, age, time to pregnancy, primary or secondary infertility, smoking, BMI, genetic familiarity for cancer, and others should be all controlled for to build solid database. To avoid the dangers of false alarms, pseudo-epidemics, and their harmful consequences, it is necessary to strive for better training of researchers, reviewers, and editors in statistics and recommend readers to be skeptic and aware of pitfalls from poorly powered studies [24].

References

1. Wainstock T, Walfisch A, Shoham-Vardi I, Segal I, Harlev A, Sergienko R, et al. Fertility treatments and pediatric neoplasms of the offspring: results of a population-based cohort with a median follow-up of 10 years. Am J Obstet Gynecol. 2017;216:314.e1–314.e14.
2. Paulson RJ. The unscientific nature of the concept that "human life begins at fertilization," and why it matters. Fertil Steril. 2017;107:566–7.
3. Shah S, Schrader KA, Waanders E, Timms AE, Vijai J, Miething C, et al. A recurrent germline PAX5 mutation confers susceptibility to pre-B cell acute lymphoblastic leukemia. Nat Genet. 2013;45:1226–31.
4. Calhaz-Jorge C, De Geyter C, Kupka MS, de Mouzon J, Erb K, Mocanu E, et al. Assisted reproductive technology in Europe, 2013: results generated from European registers by ESHRE. Hum Reprod. 2017;32:1957–73.
5. Fallah R, Jalalian MT, Golestan M, Dehghani-Firouzabadi R. Comparison of growth parameters of 5-year-old singleton children born in assisted versus natural conception. Ann Acad Med Singap. 2013;42:80–4.
6. Raimondi S, Pedotti P, Taioli E. Meta-analysis of cancer incidence in children born after assisted reproductive technologies. Br J Cancer. 2005;93:1053–6.
7. Reigstad MM, Larsen IK, Myklebust T, Robsahm TE, Oldereid NB, Brinton LA, et al. Risk of cancer in children conceived by assisted reproductive technology. Pediatrics. 2016;137:e20152061.
8. Hargreave M, Jensen A, Toender A, Andersen KK, Kjaer SK. Fertility treatment and childhood cancer risk: a systematic meta-analysis. Fertil Steril. 2013;100:150–61.
9. Hargreave M, Jensen A, Deltour I, Brinton LA, Andersen KK, Kjaer SK. Increased risk for cancer among offspring of women with fertility problems. Int J Cancer. 2013;133:1180–6.
10. Hargreave M, Jensen A, Nielsen TS, Colov EP, Andersen KK, Pinborg A, et al. Maternal use of fertility drugs and risk of cancer in children–a nationwide population-based cohort study in Denmark. Int J Cancer. 2015;136:1931–9.
11. Williams CL, Bunch KJ, Sutcliffe AG. Cancer risk among children born after assisted conception. N Engl J Med. 2014;370:975–6.
12. Williams CL, Bunch KJ, Murphy MFG, Stiller CA, Botting BJ, Wallace WH, et al. Cancer risk in children born after donor ART. Hum Reprod. 2018;33:140–6.
13. Kovac JR, Smith RP, Lipshultz LI. Relationship between advanced paternal age and male fertility highlights an impending paradigm shift in reproductive biology. Fertil Steril. 2013;100:58–9.
14. Reljič M, Knez J, Kovač V, Kovačič B. Endometrial injury, the quality of embryos, and blastocyst transfer are the most important prognostic factors for in vitro fertilization success after previous repeated unsuccessful attempts. J Assist Reprod Genet. 2017;34:775–9.
15. Meldrum DR. Aging gonads, glands, and gametes: immutable or partially reversible changes? Fertil Steril. 2013;99:1–4.
16. Meldrum DR. Introduction: obesity and reproduction. Fertil Steril. 2017;107:831–2.
17. Smajdor A, Johnson MH. I wish my mother had had me when she was younger! Reprod BioMed Online. 2015;30:441–2.
18. Falick Michaeli T, Bergman Y, Gielchinsky Y. Rejuvenating effect of pregnancy on the mother. Fertil Steril. 2015;103:1125–8.
19. Ehrlich S. Effect of fertility and infertility on longevity. Fertil Steril. 2015;103:1129–35.
20. Laufer N. Introduction: fertility and longevity. Fertil Steril. 2015;103:1107–8.
21. Levi Setti PE, Moioli M, Smeraldi A, Cesaratto E, Menduni F, Livio S, et al. Obstetric outcome and incidence of congenital anomalies in 2351 IVF/ICSI babies. J Assist Reprod Genet. 2016;33:711–7.
22. 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;366:1803–13.
23. Williams CL, Jones ME, Swerdlow AJ, Botting BJ, Davies MC, Jacobs I, et al. Risks of ovarian, breast, and corpus uteri cancer in women treated with assisted reproductive technology in Great Britain, 1991-2010: data linkage study including 2.2 million person years of observation. BMJ. 2018;362:k2644.
24. Grimes DA, Schulz KF. False alarms and pseudo-epidemics: the limitations of observational epidemiology. Obstet Gynecol. 2012;120:920–7.