The impact of ART on major malformations is not known at this time

Alfred A. Rimm · Alyce C. Katayama

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To the Editor

Hansen et al. [1] are critical of our study, [2] the primary goal of which is to raise awareness of the problem of having normal couples rather than subfertile couples comprise the control groups when estimating the odds of major malformation (MM) in the offspring of assisted reproductive technology (ART) pregnancies.

We used only one study to estimate the impact of subfertility. This was because there is only one large study which offers usable data. The fact that there is presently only one study that can be used for this purpose does not make this adjustment invalid or inappropriate because it was used only as a first estimate. At the present time, many investigators have noted that it is not possible to separate ART-related risks from those secondary to the underlying reproductive pathology. [3] Therefore we chose to work with such data as are available to make the point that there should be follow up on these ideas and that future studies should try to avoid repeating the mistake of the past regarding the use of inappropriate control groups. We may be the first to engage in a systematic effort to make this separation. We hope that future investigators will advance and refine this effort. We view our results as simply the first estimate of the effect of ART on MM rate when an appropriate control group, i.e., subfertile couples, is used.

In reviewing the comments of Hansen et al. regarding the Place study, we noted an error in calculating the OR for the Place study. We thank Hansen et al. for pointing out this error. The 1.24 which appeared in Table 1 should have been 1.33. Hansen et al. also question why the hierarchical position of some studies on the second forest plot changed even further from the original. An adjustment factor must be used when there are zero patients with MM in either the ART or control group. In our first study, a .5 adjustment factor supplied by the meta-analysis program was used. In the second study, we used a .2 adjustment factor. This change made some relative changes in the odds ratios among the studies with a small number of patients. Those with a large number of patients changed very little. This would change the ranks from study one to study two because while some studies stayed in the same relative positions, others changed slightly. The adjustment of .2 is slightly better than that of .5. The program we used in 2004 automatically adjusted using .5 because it was programmed prior to 2003. Recent research suggests that .25 is the best adjustment. This adjustment is a standard meta-analysis technique. [4, 5]

Hansen et al. question the method we used to compute the adjusted ORs when the OR was less than one. They seem to be saying that if the adjustment causes an $OR > 1$ to move closer to 1, then adjustment of an $OR < 1$ should also cause it to move closer to 1. That is not correct; after adjustment, all ORs move “downward” or to the left and if they were already less than one, they will be even further away from one. To say this another way, if the original OR was already < 1 , thus suggesting a possible protective effect, then an adjustment for the effect of underlying subfertility will reduce the OR, thus suggesting a stronger protective effect.

Hansen et al. also devise six groups within which MM rates might be measured. They then suggest that two of their

A. A. Rimm (✉)
Department of Epidemiology and Biostatistics,
Case Western Reserve University School of Medicine,
Room WG-57, 10900 Euclid Avenue,
Cleveland, OH 44106-4945, USA
e-mail: alfred.rimm@case.edu

A. C. Katayama
Health Law Group, Quarles & Brady LLP,
Milwaukee, WI, USA

six groups be used in future studies, but the studies they suggest would retain the same bias in the control groups. This suggestion repeats the mistakes of the past. To advance the study of the effects of ART in offspring, new approaches need to be used. Previous studies of this topic have used inappropriate control groups, i.e., normal couples instead of subfertile couples. In fact, lack of appropriate control groups has been identified a prominent methodological issue in studies on ART outcomes. [6–8] We recommended that future studies be designed differently to use a more scientifically valid control group.

In their final statement, Hansen et al. urge caution when counseling patients about the MM rate of ART. They suggest that patients be told that the risk is 30–40 % rather than telling ART patients that the rate of MM goes from 3 % to 4 %. Either way it is expressed, this risk estimate is derived from flawed studies based on inappropriate control groups and patients need to understand that. We suggest that patients be told that there may be little or no effect of ART on MM and that in fact ART may protect against MM.

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