

OUTCOME OF SUBSEQUENT PREGNANCIES FOLLOWING ANTIBIOTIC THERAPY AFTER PRIMARY OR MULTIPLE PREVIOUS FAILED IVF CYCLES.

PRELIMINARY ANALYSIS OF DATA OF 63 TREATED COUPLES.

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PATIENTS AND TREATMENT PROTOCOLS

63 couples with history of one or multiple previously failed IVF cycles that subsequently underwent antibiotic therapy in our center comprised the study. Success rate in subsequent IVF cycles was evaluated and compared with two recent historical controls analyzing success rates in traditional IVF cycles after one or multiple previous failures.

TREATMENT REGIMENS

Except for two couples where the husband refused any kind of cooperation in terms of antibiotic therapy, all women and all men received a ten day long intravenous Clindamycin course in continuous infusion using an ambulatory pump delivering therapeutic doses of antibiotic. During the same ten days the women received daily uterine lavages for a 50 minute period using a cocktail of a combination of Ampicillin, Gentamicin, Diflucan and Flagyl. During the same ten-day period the men received ten direct intraprostatic injections of a cocktail of a mixture of Clindamycin, Gentamicin, Diflucan, Levaquin, Zithromax and Medrol. Following this initial therapy a minimum of a month long broad-spectrum oral antibiotic course was given to both partners. Once pregnancy was reported, antibiotics were given post conception to the women and liberally used all through the course of pregnancy as dictated by the clinical condition. The choice of oral antibiotics was based on initial bacteria studies or repeat cultures taken periodically during the course of the pregnancy.

Beside minimal discomfort, no complication was encountered with either the IV, the lavages or with the prostate injections.

STATISTICAL METHODS and COMPATIVE ANALYSIS OF DATA

The primary statistical analyses were comparisons of the delivery rates for the antibiotic-treated patients with those of two different historical control samples of "conventional" IVF patients (Malizia et al., 2009; Elizur et al., 2006). This was accomplished using the Mantel-Haenszel (MH) test, stratified according to the number of previously failed cycles. More specifically, each of the published manuscripts contained tables showing the number of patients entering a given IVF cycle and the number who delivered immediately after that cycle. The number of previously failed cycles was the current cycle minus one. Based on this information, multiple 2x2 contingency tables comparing the delivery frequency of the antibiotic-treated sample with the particular historical sample were formed, each table corresponding to (i.e., stratified for) the

number of failed cycles. Since there were very few couples who had failed 6 or more cycles, therefore couples who had failed 5 cycles or more were analyzed together as one group.

The standard MH test was used, first checking for homogeneity of the odds ratios using the Breslow-Day (BD) test (SAS Version 9.1, SAS Institute, Cary, NC). In all reported analyses, the BD test was non-significant (P-values of 0.26 and 0.25, comparing to Malizia and Elizur, respectively), thus allowing for "combining" the stratified 2x2 tables according to the MH method. Due to the sparseness of many of the tables, exact 95% confidence intervals were also computed and were nearly identical to the asymptotic results; only the asymptotic results are presented. Results are reported in terms of relative risk (RR) and its associated 95% confidence interval (CI). In this report, RR represents the "risk" of a successful delivery for the antibiotic-treated group relative to the particular conventional IVF control. Accordingly, RR >1 is favorable toward the antibiotic-treated group. A result was considered statistically significant if $P < 0.05$.

RESULTS

Study group characteristics and Comparisons of Ages:

There were 63 couples in our antibiotic treated studied group with history of previous one or multiple failed IVF cycles. 12 achieved spontaneous pregnancy shortly after completing our antibiotic therapy and went through normal pregnancies and full-term deliveries. There were no premature deliveries and none of the newborns were small for gestational age (IUGR). There were no maternal or fetal complications. Out of the remaining 51 couples with history of previous failed IVF cycles (1 through 11) prior to our antibiotic therapy, 28 (54%) pursued one single IVF cycle after our antibiotic treatment and six additional couples after failing the first post antibiotic therapy repeated IVF the second time. These six couples were not considered in the calculations when the study group was matched with the historical controls publishing success rates in subsequent cycles in conventional IVF programs. The 28 patients' mean age was 38.7 (± 4.5 SD) years (Toth). The mean ages for the Malizia and Elizur studies were 35.8 (± 4.7) and 32.7 (± 5.9) years, respectively.

Comparisons of Delivery Rates:

The data used in the MH test calculations are shown in Table 1.

In both comparisons to the historical controls, the antibiotic-treated group had significantly higher delivery rates than the controls, as follows: When compared to the women described by Malizia, patients receiving antibiotics were 3.75 times more likely to deliver on the current cycle than the controls ($P < 0.0001$, $RR = 3.6$, 95% CI: 2.7 – 4.8). When compared to the controls in the Elizur publication the delivery rate was 6.35 times greater ($P < 0.0001$, $RR = 6.0$, 95% CI: 4.5 – 8.1).

PREGNANCY RELATED COMPLICATIONS AND COMPLICATIONS WITH THE NEW BORN

Both women of the two couples where the husbands refused antibiotic therapy delivered prematurely and the babies were small for gestational age. None of the other women experienced complications with the pregnancies. There were no IUGR or premature deliveries

and no perinatal fetal complications were reported. None of the newborns, including the delivered twins were admitted to NICU.

Table 1

Relative Risk of Delivery with Antibiotic Treatment Relative to Two Historical Controls

No. of Prior Failures	Antibiotic (Toth) Delivery		Malizia Delivery		Antibiotic (Toth) Delivery		Elizur Delivery	
	Yes	No	Yes	No	Yes	No	Yes	No
1	4	0	784	3053	4	0	148	1015
2	5	2	475	1753	5	2	92	657
3	6	2	221	949	6	4	50	435
4	5	0	99	474	5	0	32	300
5 or more	8	3	36	240	8	1	29	214
Totals	28	7	1615	6469	28	7	351	2621
Crude Delivery Rate	75%		20.0%		75%		11.8%	
MH Relative Risk*	RR=3.6 95%CI:2.7 – 4.8 P<0.0001				RR=6.0 95%CI:4.5 – 8.1 P<0.0001			

* MH=Mantel-Haenszel Test

Notes for Discussion:

1. Despite the fact that Toth patients' mean age was higher than either of the control groups, the pretreatment with antibiotics still gave a significantly better chance for subsequent IVF pregnancy. There was a significant chance for a post antibiotic spontaneous pregnancy.
2. Will discuss factors playing a potential role that could have caused only 28 of the 51 patients to return for a repeat post-antibiotic IVF. Similarly, only a subset of the "conventional" IVF patients ever returns for repeat IVF.
3. Addressing criticism of the statistical analysis of the relatively small group of patients since the methods used assume large sample sizes. As stated in the Methods, we calculated exact results (where large sample sizes are not required) and we got results that are consistent with the "large sample" results.
4. Our previous study, analyzing 52 treated couples using less strict antibiotic regimens showed similar significant beneficial effects of antibiotics. Combined analysis of data obtained from the recent and previous studies will further support the conclusions of our statistical analysis.
5. It is our conclusion that the only explanation for these highly significant results is that the state of the uterus at the time of conception, more precisely the bacteria content of the uterus, will determine the course and outcome of the pregnancy and can gravely affect the health of the new-born.
6. The uncomplicated pregnancies and the healthy babies born after antibiotic therapy will help reduce long term healthcare costs.