Outcome Of Subsequent Ivf Cycles Following Antibiotic Therapy After Primary Or Multiple Previously Failed Ivf Cycles

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Abstract

Objective: To determine whether broad spectrum antibiotic therapy given to couples following a failed IVF cycle will improve the chance of achieving a successful pregnancy in the subsequent IVF cycle.

Design: In an academically affiliated private infertility center retrospective analysis of clinical data of 52 couples who previously failed one or multiple IVF cycles and subsequently was treated with broad spectrum antibiotics was carried out. All females were treated with intravenous Clindamycin combined with intrauterine lavages using a broad spectrum antibiotic combination. 26 males received intravenous Clindamycin and for those who declined, Augmentin 875 mgs twice daily for fourteen days was substituted. For both males and females theses regimens were followed by oral doxicycline, 100 mgs twice daily for three weeks.

Results: There was a significantly improved chance for the couples to achieve a successful pregnancy following antibiotic therapy when compared with historical controls in conventional repeat IVF cycles. Except for one case of preeclampsia, there was no other pregnancy-related complication. Cesarean section was performed on an elective basis, none of the newborns suffered from IUGR. For the 19 deliveries there were 24 neonatal ICU days, all but four for the twins' and triplets' deliveries. For singleton pregnancies, there were no perinatal maternal or fetal complications.

Conclusion: These findings suggest that a certain number of failures during IVF cycles are due to an intrauterine infection that could affect the course of the pregnancy, the mode of delivery and cause maternal and fetal complications.

INTRODUCTION

While improvements in IVF technology have offered numerous infertile couples the chance to achieve a successful pregnancy. The per cycle success rate in most clinics hovers around 25% ([1], [2]) and the chance for a successful outcome diminishes with subsequent trials. The cumulative live birth rate after seven IVF cycles is around 60% ([3],[4],[5],[6]). Some of the failures are attributed to male factor ([7]), poor oocyte quality ([8]), reduced ovarian reserve ([9]), uterine problems ([10]), and chromosomal abnormalities of the embryos ([11]). In general, advanced maternal age is associated with a poorer outcome ([12]). The role of infections is also appreciated and most IVF cycles are complemented with a limited oral antibiotic regimen ([13],[14],[15],[16]). In a high percentage of cases, however, the cause of failure remains unknown. In addition there are only speculative explanations why IVF pregnancies are more often complicated by premature birth, intrauterine growth retardation and chromosomal abnormalities than naturally conceived pregnancies ([17],[18],[19]).

Two decades of favorable experience with antibiotic therapy, initially given orally, later administered intravenously with uterine lavages, both in terms of reversing infertility and improving pregnancy outcome, prompted us to offer broad spectrum antibiotic therapy to couples who have failed one or multiple IVF cycles and were ready to return for subsequent trials ([20], [21]). We report our experience here with the first 52 couples that were treated at our clinic between 01/01/2002 and 04/01/2004.

MATERIALS AND METHODS

STUDY DESIGN

A retrospective chart analysis and telephone follow up was carried out on 52 couples who were treated at the MacLeod Laboratory between January first 2002 and April first 2004. The Institutional Review Board of New York Presbyterian Hospital approved the study. Informed consent was obtained from the patients for data collection, analysis and publication conforming with local and national regulations. The authors had full access to the data, directed the data analysis, and were responsible for decisions regarding publication. The principal investigator (Dr. Toth) assumes full responsibility for the integrity and interpretation of the data.

PATIENTS

A total of 52 consecutive couples with history of primary or multiple previously failed IVF cycles that were referred to us through different infertility websites or through direct patient referral for antibiotic therapy were eligible for the study. Before initiating the antibiotic therapy both husband and wife underwent serum antisperm antibody testing using immunobead technique. Cervical and endometrial cultures on the females and seminal fluid and urethral cultures on the males were performed. Chlamydia trachomatis was tested for using the Pathfinder Direct Antigen Detection System from Bio-Rad Laboratories, A7 differential agar was used to identify Mycoplasma, and API systems were used for aerobic bacteria identification. Ramel Rapid Ana II system was used to identify anaerobic bacteria and the API 20c AUX system was used to identify yeast. The Rapid NH System identified Neisseria and Haemophilus. Trichomonas vaginalis was identified after overnight growth in a selective broth. (In Pouch TV test Kit). The result of the culture studies did not influence the recommendation of antibiotic therapy. All females were treated with a combination of ten days of intravenous Clindamycin in full therapeutic dose, typically, 900 mg every 8 hours for an individual of 150 lbs body weight, and five intrauterine lavages performed on consecutive days of the first five days of IV therapy. The lavages applied a mixture of 6 grams ampicillin, 160 mgs gentamicin, 4 mgs fluconazole (Diflucan), and 10 mgs metronidazole delivered one-hour daily using an ambulatory pump and a Cook 5.3FR intrauterine catheter. At the end of each lavage the uterine cavity and cervical canal were filled with a 20% metronidazole containing gel prepared by a local pharmacy. Following this, a three-week oral doxycycline course, 100 mgs twice daily, completed the treatment course. Similarly, intravenous Clindamycin was offered to the males (26 patients) and for those who declined the intravenous antibiotic, Augmentin 875 mgs twice daily for fourteen days was substituted. For both groups, this regimen was followed by oral doxycycline, 100 mgs twice daily for an additional three weeks. Except for two cases of mild diarrhea, which responded promptly to oral metronidazole, no other complications were encountered with any of the antibiotic treatment modalities.

STUDY PROCEDURE AND END POINTS

Reproductive events following the completion of the antibiotic therapy were gathered through a direct telephone interview up to a successful pregnancy or if a successful pregnancy did not occur, up to a maximum of 18 months.

STATISTICAL METHODS

Using three published studies, all with large number of cases and a high order of IVF cycles Osmanagaoglu K. et al. ([5]), Lass A. et al ([12]) and Witsenburg C. et al ([6]), the primary statistical analyses were comparisons of the delivery rates for the antibiotic-treated patients with those of three different historical control samples of “conventional” IVF patients. 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. (For calculation purposes, the number of previously failed cycles was the current cycle minus one.) Similarly, for patients treated with antibiotics prior to an IVF cycle, an outcome was counted as a “delivery” only if the patient conceived and delivered immediately after the IVF cycle corresponding to the pre-treatment with antibiotics. Based on this information, multiple 2x2 contingency tables comparing the delivery frequency of the antibiotic sample with the particular historical sample were formed, each table corresponding to (i.e., stratified for) the number of failed cycles. For the few patients with more than 6 previously failed cycles, the corresponding data were aggregated into a table indexed as “6 or more failed cycles”. For this analysis the four spontaneous pregnancies were excluded from all calculations, since the control publications counted such pregnancies as “drop outs” and were not included in their calculations.

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

ranging from 0.24 to 0.83), thus allowing for "combining" the stratified 2x2 tables according to the MH method. Due to the sparseness of many of the tables, exact MH tests were also carried out with nearly identical results (StatXact, Version 3.0.2, Cytel Software, Cambridge, MA). In cases where a published result was restricted to a certain age group, the antibiotic-treated group was also restricted to that age group. 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. A result was considered statistically significant if $P<0.05$.

Since the distribution of "number of prior failures" differed for the antibiotic-treated group relative to each of its comparators, the crude delivery rates are not comparable. To make the rates comparable, the delivery rates for the antibiotic group were standardized to that of each respective comparator using the so-called "direct standardization method"([22]).

RESULTS

DESCRIPTION OF THE ANTIBIOTIC-TREATED COHORT:

Table 1 shows the demographic, clinical, and pregnancy outcome profiles of the antibiotic-treated group of patients. With the exception of age, statistics for these variables were not available in the published papers used for comparison.

Figure 1

Table 1: Characteristics of IVF Patients Treated with Antibiotics (ABtx)

Characteristic	All patients (n=52)	Spontaneous pregnancy after ABtx (n=4)	Successful 1st IVF pregnancy after ABtx (n=16)	Successful 2nd IVF pregnancy after ABtx (n=3)
Age (years) (mean±SD)	38.5 ± 4.2	36.8 ± 2.8	39.3 ± 3.9	36.0 ± 4.4
Length of infertility (years)	4.7 ± 2.1	3.3 ± 0.5	4.9 ± 1.5	4.7 ± 2.5
Type of Infertility				
Ovulatory	10 (19.2%)	1 (25.0%)	1 (6.3%)	2 (66.7%)
Endometriosis	2 (3.9%)	1 (25.0%)	0 (0.0%)	0 (0.0%)
Uterine factor	1 (2.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Tubal factor	12 (23.1%)	1 (25.0%)	4 (25.0%)	0 (0.0%)
Male factor	6 (11.5%)	0 (0.0%)	3 (18.8%)	0 (0.0%)
Unknown	21 (40.4%)	1 (25.0%)	8 (50.0%)	1 (33.3%)
Pregnancy Outcomes				
Length of gestation (days)	n/a	275.5 ± 20.5	267.7 ± 16.3	264.7 ± 5.1
Vaginal, C/S delivery (%)	n/a	2/2 (50.0%)	5/16 (31.3%)	0/3 (0.0%)
Birth weight of singleton newborns (grams)	n/a	3565.8 ± 645.4	3441.0 ± 462.1**	3520.5±712.1*

* n=2 singletons; one patient delivered twins
** n= 14 singletons, one patient delivered twins, one delivered triplets

COMPARISONS OF AGES

There were 52 patients studied in the antibiotic-treated group. The average patient's age was 38.5 (± 4.2 SD).

The Osmanagaoglu historical control group consisted of women over 37 years old (mean 40.1, no SD given). When the antibiotic-treated group was restricted to over 37 years old, the mean age was 41.2 ± 2.7 years.

The group studied in Lass was 40 years and older.

The Witsenburg sample was more general with a mean age of 33.0±4.0 years (compared to 38.5 ± 4.2 in the antibiotic sample).

COMPARISONS OF DELIVERY RATES

In all three comparisons to historical controls, the antibiotic-treated group had significantly higher delivery rates than the controls.

When compared to those women greater than 37 years old in the Osmanagaoglu publication, patients receiving antibiotics were 4.5 times more likely to deliver on the current cycle than the controls ($P<0.0001$, RR=4.5, 95% CI: 2.1-9.5). The delivery rate for Osmanagaoglu was 7.2% and the standardized rate for the antibiotic group was 46.1%.

When compared to the controls in Lass publication, the delivery rate was 12.5 times greater (P<0.0001, RR=12.5, 95% CI: 4.5-34.8). The standardized delivery rates were 6.4% for Lass and 54.8% for the antibiotic group.

Even the comparison with a considerably younger patient group, the Witsenburg controls resulted in a significantly improved chance for pregnancy of 1.7 (P<0.0302, RR=1.7, 95% CI: 1.1-2.6). The respective standardized delivery rates were 22.8% and 33.8%.

Figure 2

Table 2: Relative Risk of Delivery with Antibiotic Treatment Relative to Three Historical Controls

	Antibiotic (Toth)		Osmanagaoglu [a]		Antibiotic (Toth)		Lass [b]		Antibiotic (Toth)		Witsenburg [c]	
No. Prior Failures	Delivery***		Delivery		Delivery***		Delivery		Delivery***		Delivery	
	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
1	3	3	5	98	2	3	13	181	5	6	136	357
2	1	1	4	52	1	0	5	62	1	6	64	235
3	4	5	3	24	4	2	1	23	4	8	23	128
4	1	2	2	11	1	8	0	10	4	4	11	62
5	0	2	1	5	*	*	*	*	0	2	7	32
6 or more	1	6	0	4	*	*	*	*	2	6	3	11
Totals	10	19	15	194	8	13	19	276	16	32	244	825
Crude Delivery Rate	34.4%		7.2%		38.1%		6.4%		33.3%		22.8%	
Adjusted Delivery Rate**	46.1%		7.2%		54.8%		6.4%		33.8%		22.8%	
MH Relative Risk	RR=4.5 95%CI: 2.1-9.5 P<0.0001				RR=12.5 95%CI: 4.5-34.8 P<0.0001				RR=1.7 95%CI: 1.1-2.6 P<0.0302			

* Due to small numbers, data for "5" and "6 or more" prior failures have been aggregated with "4" to become "4 or more".
** Direct standardization with respect to "number of prior failures" distribution of comparator.
***Spontaneous pregnancies (n=4 total) excluded from all frequency counts and analyses
a: age > 37
b: age ≥ 40
c: all ages

DISCUSSION

Published clinical trials showing either the beneficial effect of antibiotics or no effect at all on improving IVF pregnancy rates all used limited courses of orally administered antibiotics ([23,24]).

This study shows that broad-spectrum antibiotics given in the form of intravenous administration combined with intrauterine lavages greatly improve a woman's chances to achieve a subsequent spontaneous or IVF pregnancy. We conclude therefore that at least in a subset of IVF failures a direct uterine infection plays a role. In our series, following antibiotic therapy, up to age 43 there was no significant decline in the woman's chance of achieving a subsequent pregnancy suggesting that in certain cases it could be a low-grade bacterial contamination of the female reproductive canal that renders women of all ages sub fertile and has a cumulative disproportionate effect on women above forty. We concur with other investigators who find Chlamydia to be a significant pathogen. The high isolation rate of Chlamydia in our patient population is troublesome and warrants explanation. We have encountered several patients where IVF was initiated without prior Chlamydia screening. In cases where previous screening has been performed and therapy given for Chlamydia infection we assume the presence of a resistant strain rather than a reinfection. We are aware of the emergence of multiple antibiotic-resistant Chlamydia strains and encountered a number of cases where long, broad-spectrum antibiotic therapy courses failed to eradicate Chlamydia ([25,26]).

Neither the pretreatment Chlamydia positive culture status nor the total number of pretreatment bacterial isolates was predictor of a successful pregnancy. Moderately or significantly elevated male antisperm antibody levels seem to relate to fewer successful deliveries. The small sample size however prevents a significant conclusion (Table 3). Clearly, more detailed microbiological and immunological studies are indicated.

Figure 3

Table 3: Examined immunological and microbiological findings in the delivered and none delivered groups

		No Delivery (n=33)		Delivery* (n=19)	
Chlamydia status (Male or female)	Negative	18	66.7%	9	33.3%
	Positive	15	60.0%	10	40.0%
Total Number of bacteria isolated (mean ± SD) (Male or female)		2.8 ± 1.6		2.8 ± 1.7	
Antibody male	None	9	56.3%	7	43.7%
	Mild	10	55.6%	8	44.4%
	Moderate	8	80.0%	2	20.0%
	Severe	6	75.0%	2	25.0%
Antibody female	None	12	57.1%	9	42.9%
	Mild	11	91.7%	1	8.3%
	Moderate	6	60.0%	4	40.0%
	Severe	4	44.4%	5	55.6%

* Total deliveries is 19, which includes 16 deliveries in the cycle immediately after antibiotic therapy, and 3 deliveries after a second IVF cycle following antibiotics.
No significant associations were found.

In general, IVF pregnancies have an increased risk of developing pregnancy-associated complications, such as bleeding, preeclampsia, placenta previa, premature rupture of membranes (PROM) and preterm delivery. Interventions, including cesarean sections and induction of labor are more frequent. The newborns conceived through an IVF cycle have a higher chance of being extreme low or low birth weight and suffer from intrauterine growth retardation ([27,28,29]).

In our series none of the patients delivered extremely prematurely and none of our babies were of extremely small weight and there were no intrauterine growth retarded newborns. Our series lacks the complicated pregnancies and the deliveries of sickly children. The four NICU days spent by our singleton newborns in hospitals were for observation only. Despite the failure of microbiological studies to show a difference between those patients who failed or succeeded in subsequent IVF cycles we attribute this favorable outcome to the antimicrobial effect of the antibiotics and postulate that at least in some of those cases where IVF pregnancies are associated with premature delivery, IUGR, extreme prematurity, maternal and fetal infectious complications and the need for NICU admission, an intrauterine infection is at play and most likely this is the same infection that has rendered the woman infertile and in need of the IVF procedure to start with.

It is tempting to postulate that the common observation that IVF pregnancies yield individuals with an increased number of medical problems that result in higher health costs in the future ($_{30}$) could be due to the mothers' infected uterine environment. Thus preventive medicine in the form of antibiotic therapy prior to the first IVF attempt could contribute to a reduction in future health costs.

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