Dialogue with the Stalwart

Interview with Dr.B.N.Chakravarty

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Dr.B.N.Chakravarty

We have heard about your great love for teaching, Sir. So what has been your inspiration to join this field?

Initially, I didn't have much interest to join this IVF discipline, I was working as a clinician, as a gynaecologist and obstetrician, doing surgeries partly related to infertility. I was doing a lot of oncology surgery. In 1970's, there was no radiotherapy, or chemotherapy, so I had to do oncology radical, ultraradical surgeries. But that did not give me an incentive as the results were not very good. While doing that I learned the technique of fine dissection of the tissues, so I moved on to congenital malformation of the female genital tract, because that was also an area that was not touched upon by the ordinary gynaecologists.

I saw a case; a small girl coming with primary amenohorrea, of 15-16yrs, the defect was absence of vagina, absence of uterus; at a stretch I had to construct the uterus because of absence of mullerian knobs. For all these young girls of 13-15yrs there was no treatment available. So I took up those cases and started doing re-constitutive surgery, very few reports were there all over the world. I could do re-constitutive surgery of the vagina which went quite alright,and united the two mullerian knobs inside the pelvis with the hope that they will menstruate and finally have a pregnancy. In 1967-68, I presented that paper in Switzerland. It worked well as far as menstruation was concerned, but they didn't have a pregnancy. There is another type of malformation simultaneously seen in these patients, that they had an uterus but not the lower part of the genital tract i.e, the cervix was absent, the vagina was absent.

So I could at least restore the sexual function by creating a vagina, but the menstrual function was absent. They had a functioning uterus and they had the menstrual function as well but invariably, in majority of these girls, cervix used to be re-stenosed, re-operated, so for some or the other reason it went on for some time but finally around 2 girls conceived. I did around 25-30 surgeries on such cases. Until the age of 70 or 75, I went on doing these surgeries and almost all of them had menstrual cycle re-established but 3 of them got pregnancy. That was reported in American Journal of Gynaecology in 2000.

During that period I came in contact with Dr.Subhash Mukherjee. I was presenting and publishing all these papers in scientific conferences when he heard about me. He created an interest in fertility in me and that is how I joined this field. While I was trying for a pregnancy after a surgical correction, he was trying for pregnancy after medical treatment. He was a physiologist, not a gynaecologist. We were both in Govt. Medical service. In one institute, the NRS medical college we were posted together, he was the Asst. Professor of Physiology and I was the Asst. Prof. in Obstetrics & Gynaecology. So we used to hold meetings very frequently, and gather all these cases; from my side all the congenital abnormalities and on his side, Turners syndrome, testicular feminizing syndrome, PCOS, and congenital adrenogenital hyperplasia. Every week we used to run a clinic and about 30-35 patients used to come there. We used to do investigations, give medical treatment and gradually that made me interested. I had no idea about endocrinology because I was a very blunt cutter, but he created interest in me.

Anyway, at that time in 1974-75, Dr.Mukherji was reading journals with publications of Dr.Steptoe and Dr.Edwards and he used to talk about test tube baby of which I had no idea at that time. We went to Tokyo,Japan together, for a world conference where I presented my paper on hysteroplasty, vaginoplasty and he presented his paper on stress induced PCOS. Anyway, both of our papers were appreciated in that conference and it appeared in journals and papers also, it came out very well in the conference bulletin saying that, from India, two papers have come and were applauded very much. Later he published a paper reporting the birth of a test tube baby, Durga, on Oct 1978, 3 months after the test tube baby in England, Louise Brown, that of Robert Edwards and Steptoe. Till 1978, he was criticized all over the country, all of us know that tragic story. He got very depressed because of all things coming up, and finally committed suicide. After that his wife came to me asking to carry on his work and that people should not call him a liar. I promised to continue his work and that was how I entered into the field of IVF, not intentionally but circumstantially.

When I was invited to deliver lectures outside, in India and abroad, people did not believe my work and started doubting me which was very upsetting. But that gave me strength, I took it up as a challenge and wanted to prove that it can be done in India. So I formed a team with young doctors and started the work together. At that time, nothing was available in India, not even the embryo transfer catheter, not to speak of the culture media. We did not know about the media, nor about the CO_2 cylinder.

Your team had developed a new technique for a CO_2 incubator back then.

Yes, we used to pump in our exhaled air to the embryo culture as exhaled air contains CO_2, and the oxygen from the oxygen cylinder. There was a baby incubator, but that did not bring us success as the embryos used to become dark. The media was not available; we started with Tyrode's media and Hams F12 was available in Mumbai, for which we used to travel to Mumbai to get, and even the MilliQ water was not available. We used to prepare the media ourselves. So, from Bangalore, we got the Millipore filter and started filtering. That was our beginning. We started reading endocrinology voraciously. I still remember the book, Ganong's; it was very basic and interesting book. But for the equipment and consumables we faced a lot of trouble as we could not import anything during those days without an import license. For plastic materials alone at that time, we used pay tax of 300%.

In 1982-83, the first international conference was held in Helsinki, Finland, where I presented a paper along with my embryologist. My paper was accepted there. We presented the first cleavage embryo that resulted in a biochemical pregnancy. The first baby was born in 1986, Imran , the first viable baby.

Ever since you have achieved a lot over the years.

Yes, I devoted myself to IVF, I gradually gave up even Gynaecology. We formed a very good team and they supported me like anything. After we got the first test tube baby the government supported us by alloting an area, a very calm place, it was more or less a car garage, in which we turned into laboratory, In 1992 we got some freedom; we got the import license when Manmohan Singh was the finance minister. Until then it was hush-hush type of experience, and the patients also were very scared. They used to hide that it was a test tube baby. In the society that was not accepted back then.

Even India's first IVF baby, Durga, was also kept secret for a long time.

There was always a belief that for a test tube baby, semen always came from a donor. I don't know wherefrom that false, erroneous concept came. That was one of the major difficulties we faced.

How did your interest come about in antioxidants for male infertility, to increase sperm production?

We got a luminometer and measured the pro-oxidants, and oxidative stress on asthenozoospermic subjects, we could count the limit of stress. And we used to add vit.E, vit.C, and Apo co-enyzme and see remarkable improvement in vitro. We have done a study which we will be publishing in next ISAR. We were using both nutraceuticals and anitoxidants but while using in vivo, no improvement was achieved.

What do you think about multiple drugs, like lycopene, arginine, carnitine, used for male infertility?

They are still empirical. Each of the antioxidant has different functions, some provide nutrition, some provide metabolic functions, some provide metabolic respiratory function, and some of them provide locomotion. These functions must be there, following which, the sperm can fertilize. The sperm has a long way to travel, from the seminiferous tubules to the fallopian tubes; there are so many turbulences on the way, but the function should remain intact during these turbulences. Unless the DNA is compact it cannot withstand all the turbulences on the way. And it must remain active. For this activity you require antioxidants.

ICSI used to be done for severe male infertility, but nowadays ICSI is done for all patients, do you feel IVF has started deteriorating, going the GIFT way?

Not everybody believes in that particular dictum – 'All ICSI, no IVF'. Though we have no particular evidence, ICSI may do some damage. Afterall, it is an invasive procedure, and a non-selective procedure. Always there's a sperm selection, and there are 4 stages of sperm selection – vagina, uterine tract, cumulus corona mass and zona pellucida. The best sperm, most vital sperm must fertilize the oocyte.

And that is surpassed in case of ICSI. ICSI does not believe in that. They are of course trying to isolate the best looking sperm, but only morphologically, no biochemical tests are done. In all the sperm function tests, nothing is biochemical, excepting HOST. Nowadays we have IMSI, PICSI, but still not the best sperm can be selected. But you are getting pregnancies, and babies also do not have any congenital defects; so though there are so many arguments against ICSI, you cannot prove that ICSI is bad.

But all the first ICSI babies are reaching the reproductive age only now. So only now will we get to know if they are normal. What about your IVF baby, Imran, he must be around 27 now, is there still a follow up?

Yes, I heard he got married and he's got a child now. But he's not keeping in touch with us, for the same reason. Those days, the prejudice was there, he was from a village and his mother was afraid that the people will think he's not her boy, or they wouldn't have used her husband's sperm. And our next baby in1989, Suraj, was from Kerala, he's also very good, as far as intelligence is concerned, but he's still in college.

Which do you feel is better, Day 3 embryo or Day 5 embryo? Your view.

It all depends; day 3 and day 5, both are good. Two points must be highlighted, one being the quality of the embryology lab, that must be very good and the second one is the patient and cycle characteristics. The cycle characteristics are that in that particular cycle, how many eggs were retrieved and on day 3 how many eggs have gone upto 10cell stage? So if more than 2 have gone, then I think day 5 can be done. Less than three is better to do day 3.

Nowadays, people have started to follow 'freeze all' technique for embryos, your opinion.

The dictum is coming, but I am not very sure. The same thing follows, the quality of the lab, you must be very confident of the culture lab and also about your vitrification procedure, and the recovery rate. And our recovery rates are not as good as what have been suggested by the papers. In my lab, I would not allow that unless I am very confident.

Suppose you were very confident, then would you go ahead.

Yes, theoretically, it holds good. In a stimulated cycle, the quality of the endometrium is not that good as the natural cycle, so that holds good. But there are some objections, opposing that, even in presence of high levels of progesterone and estradiol, the pregnancy rate is not bad. But the consensus is, in a stimulated cycle the endome trium is antedated and not coinciding with the blastocyst formation.

In cases of unreceptive endometrium, do you think assays like Endometrial receptor assay(ERA) will be useful?

No, I don't think it is of any practical use; theoretically, yes. Since the endometrial bit is taken in the pre-conception cycle and not the treatment cycle, it does not hold good. And you cannot take in the treatment cycle as it might disturb the endometrium. But there is an opinion for that, traumatizing the endometrium in the pre-conception cycle will bring out better receptivity. But I have no confidence in that. To touch the endometrium during the conception cycle is very risky, and the endometrium varies cycle to cycle, and genes expressing will vary, the steroid level also varies, and it would depend on the nature of stimulation given. They are all vague areas, which have to be explored by non-invasive methods.

We are trying to get non-invasive markers, we are currently working on uterine fluid, maternal serum and follicular fluid. Follicular fluid will be the best marker because I believe that good oocyte will produce a good embryo and a good embryo through dialogue with the endometrium will give better receptivity. A good oocyte will develop in good environment and good environment is good follicular fluid, so the markers of the follicular fluid can predict if it is a good oocyte or bad oocyte. Similarly, AMH, estradiol, IGF-1,plasminogen are good markers,MMP, all these markers, we are trying to correlate them, with pregnancy. The follicular fluid is a gold mine.

The drugs used for stimulation, would you prefer urinary or recombinant?

That is more or less clarified, excepting preconditions like over down regulatory cycle, or long protocol down regulation, in that case any drug you can use, over down regulatory cycle you have to use HMG, and LH and second one is poor ovarian response, you also require some LH, and in elderly ladies with less amount of testosterone which means less amount of LH, these are the 3 groups of patients who require a definite initial stimulation with urinary HMG, rather than recombinant FSH/LH. In normal responders, you have a choice, FSH is better, I think.

As for your achievement of conception in a 50 yr old lady which was reported in the news recently?

That is another area which we are working, recurrent implantation success as against recurrent implantation failure, which is a common thing. Not only this lady, before this we had another lady who had 10 times implantation, she was getting pregnant every time, but the pregnancy was not going to term. This 50yr old lady also, she had two attempts, the first attempt also was an implantation success, but it ended in a miscarriage at 8-10wks. The second time also she got pregnant. So she was a woman with a favorable embryo and favorable endometrium, clicking together. So we are thinking that there must be a difference between the couples, in the whole society. Some couples conceive within the first month of marriage, some couples take six months, why is this difference? They do not use any contraceptives or fertility improving drug, and yet do not get pregnant. This fertility index also exists in infertile patients. We are trying to get genomic or metabolomic differences between these couples of recurrent implantation success and recurrent implantation failure.

In today's practice, everyone is doing sperm DNA integrity test and they are giving medications accordingly, what is your view? Is it worthwhile conducting the test?

I have no idea. Practically it is not possible. Excepting for IMSI, All the other tests are biochemical in which we'll be losing the sperm.

ART guidelines then and now.

I am not very happy. Back then we started the guidelines so that people will follow it strictly, but it is not being followed at all. Especially, they are playing with the third party reproduction, the oocyte donor and surrogacy. It has become a business.

What does the future hold for ART?

It will be very good. Barring some areas, it is opening up so many things, particularly in the field of male infertility, endometriosis, endometrial receptivity. You know the problem but you don't have the solution, so proteomics and genomics will help us.

What would be the advise you would give for all your students?

Teaching is a habit, and by teaching you learn, you rectify your mistakes. No teacher has 100% knowledge. In one word, self audit- don't think you know everything. You learn by teaching; when you stand on a dais and talk there are some areas you would not be able to explain. This makes you think if there is some deficiency in your knowledge or deficiency in your expression. No one can teach you that. You have to learn it yourself.