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CASE REPORT

INFERTILITY MAY SOMETIMES BE ASSOCIATED WITH NSAID CONSUMPTION

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SUMMARY

Non-steroidal anti-inflammatory drugs are widely used in the treatment of inflammatory joint diseases. Many patients suffering from these disorders are young women during their childbearing years. We report three cases of infertility where the cause may have been NSAID-induced 'luteinized unruptured follicle' syndrome. This phenomenon is well recognized in obstetric circles, and we would like to bring it to the attention of rheumatologists since it is not documented in the rheumatological literature.

KEY WORDS: NSAID, Infertility, Luteinized unruptured follicle syndrome.

IT is debated whether women with inflammatory joint disease or connective tissue disease are less fertile than the rest of the population. Any subfertility, if it exists, is generally thought to be related to disease activity. Nevertheless, many patients suffering from these disorders are young women during the childbearing years, and some will have difficulty becoming pregnant whatever the cause. We report three cases.

CASE 1

A 20-yr-old Caucasian woman first presented in December 1984 with a year history of back pain, radiating to the left buttock and posterior thigh. She had not gained any relief by various forms of treatment including osteopathic mobilization, spinal injections and local physiotherapy. Indomethacin helped her symptoms a great deal, but she had to take 50 mg four times daily for adequate relief. In the past medical history, she had had iritis at the age of 16. During that year, she had a hot swollen red tender ankle joint which settled with indomethacin.

Physical examination was unremarkable. Pelvic X-ray showed sclerosis of the left sacroiliac joint. The erythrocyte sedimentation rate (ESR) was raised at 48 mm/h and HLA B27 was positive. A diagnosis of ankylosing spondylitis was made and she was advised to continue taking indomethacin. She failed to attend follow-up appointments.

In February 1990, she was referred by her general practitioner with a 2 yr history of primary infertility despite normal coitus. She had been on the oral contraceptive pill for 7 yr before marriage and had come off the pill 3.5 yr previously. She was on indomethacin slow release 75 mg twice daily. Her periods were regular and normal. No abnormalities were found on examination.

Her husband was 26 yr of age, and had no significant medical history. His physical examination was also normal.

The ESR was 8 mm/h. Serum prolactin and thyroxine were normal. Mid-luteal progesterone levels were in the low post-ovulatory range, although her basal body temperature chart had features typical of ovulatory cycles. Her husband's sperm analysis was satisfactory. Laparoscopy and dye test were arranged, but the patient failed to attend.

She returned to clinic 6 months later. She was commenced on clomiphene. Day 21 serum progesterone suggested ovulation, with a level of 45 nmol/l (luteal phase reference range 10–64 nmol/l). Six months later, clomiphene was discontinued because the patient was no longer keen on getting pregnant due to her husband's unemployment. After a further 8 months, she returned for further investigations and a laparoscopy was carried out. This showed a normal uterus, ovaries and tubes with no adhesions. There was grade 1 endometriosis with small deposits on the uterosacral ligaments, round ligaments and near the ovaries.

There was bilateral fill and spill of dye. She was commenced on danazol which was continued for 6 months.

The possibility of a luteinized unruptured follicle syndrome was considered as a cause of her infertility. *In vitro* fertilization (IVF) was thought to be the best treatment as she was unlikely to stop anti-inflammatory treatment. Indomethacin was changed to diclofenac, which she discontinued 2 months later because of dyspeptic symptoms. Within 3 weeks of stopping treatment, she became pregnant spontaneously without any need for IVF.

The striking time relationship and the absence of any significant pathology would suggest that the non-steroidal drugs may have been playing a part in her case.

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CASE 2

A 32-yr-old woman was referred in September 1991 with an 18 month history of a painful stiff neck and a painful swollen right knee over the past few weeks. Her symptoms began shortly after the delivery of her daughter. Her brother had bilateral total hip replacement and cannot move his neck, and her father received radiotherapy for his spine during his youth. She has been treated with relatively small doses of naproxen, diclofenac and coproxamol.

Examination showed restricted movements of cervical and lumbar spine, right hip and both shoulders. X-rays showed bilateral sacroiliitis, anterior fusion of the vertebral bodies of C2, C3, C4, C5 and significant loss of right hip joint space. The ESR was 74 mm/h. A diagnosis of ankylosing spondylitis was made and she was commenced on diclofenac slow release 100 mg daily, and started an intensive physiotherapy programme. She made a remarkable improvement with no further pain or swelling.

In May 1993, she was referred by her general practitioner to the Department of Gynaecology with a 27 month history of secondary infertility. Her day 21 progesterone level was in the ovulatory range, but suboptimal at 18.4 nmol/l.

Her other endocrine tests were unremarkable and a hysterosalpingogram showed a normal uterus and tubes. It was thought that diclofenac was responsible for her secondary infertility and was therefore discontinued. Her 21 day progesterone level improved to 59.6 nmol/l and a month later she became pregnant.

CASE 3

This 33-yr-old woman had rheumatoid arthritis for 9 yr. Diclofenac (200 mg daily) and sulphasalazine were commenced on presentation, hydroxychloroquine was added 4 yr later. She was investigated for a 2 yr history of infertility and was found to have elevated prolactin levels, but no pituitary tumour. Bromocriptine was suggested. However, diclofenac was stopped at this stage (hydroxychloroquine was also stopped a few weeks earlier). Within days, and before starting the bromocriptine, she became pregnant.

DISCUSSION

It is recognized in obstetric circles that NSAIDs may play a part in contributing to infertility, and we would like to bring this to the attention of rheumatologists since it is not documented in the rheumatological literature.

The luteinized unruptured follicle syndrome is a phenomenon whereby normal ovarian follicular development is followed by a pattern of serum concentration of progesterone compatible with ovulation and yet the cycle remains anovulatory because the follicular wall remains unruptured. The phenomenon occurs intermittently in the general population, but more frequently in women complaining of infertility [1].

The action of NSAIDs in preventing follicle rupture has been used deliberately to delay follicle rupture in order to harvest eggs from the follicles for IVF.

In rats [2] and rabbits [3], the use of the prostaglandin synthetase inhibitor, indomethacin, reproduces the syndrome.

In 1987, Killick and Elstein [4] performed serial ultrasound scans of follicular development throughout 46 spontaneous cycles in 20 healthy female volunteers. Human chorionic gonadotrophin was then given to induce follicular rupture on a particular day. Luteinized unruptured follicles (LUF) were seen in 10.7% of untreated cycles. When prostaglandin synthetase inhibitor drugs were administered over the ovulatory period, the incidence of LUF was greatly increased (to 50% with azapropazone and 100% with indomethacin). Serum oestradiol concentrations and the length of the luteal phase were unaltered in LUF cycles. Progesterone concentrations were, however, lower in the first half of the luteal phase if follicles remained unruptured.

In our patients, indomethacin and diclofenac seemed to be the offending agents. The striking time relationship between withdrawal of NSAIDs and becoming pregnant, all within one menstrual cycle, and prolonged previous history of infertility, all over 2 yr, in the absence of any other convincing cause, strongly suggest that NSAIDs were implicated in the infertility.

In our patients, where the investigations were carried out, the implication seemed to be that ovulation was probably occurring and yet conception did not take place until after the withdrawal of NSAIDs.

There is no evidence to suggest that the ranges of NSAID currently in use are teratogenic and therefore contraindicated in people attempting pregnancy or in the early stages of pregnancy although, of course, there is good evidence to suggest that they should be withdrawn in the later stages of pregnancy because of possible effects on parturition itself and physiological changes taking place at birth, and before it, in the child. The possibility, however, that NSAIDs may in at least a few cases contribute to infertility should suggest that attempts at NSAID withdrawal should occur either before or concurrent with the simpler investigations for infertility before any more complicated procedures are considered.

CONCLUSION

The potential contraceptive effect of NSAIDs should be remembered when prescribing these drugs to women during their childbearing years.

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