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World Journal of Obstetrics and Gynecology
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: +86-10-85381891
Fax: +86-10-85381893
E-mail: wjog@wjgnet.com
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Fax: +852-65557188
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REVIEW

New developments of the effect of melatonin on reproduction

Fanuel Lampiao, Stefan S Du Plessis

Fanuel Lampiao, Division of Physiology, Department of Basic Medical Sciences, College of Medicine, Blantyre 3, Malawi
Stefan S Du Plessis, Division of Medical Physiology, Stellenbosch University, Tygerberg Campus, Tygerberg 19063, South Africa
Author contributions: Lampiao F and Du Plessis SS were involved in conception and designing, drafting, revising and final approval of the article.
Correspondence to: Fanuel Lampiao, PhD, Division of Physiology, Department of Basic Medical Sciences, College of Medicine, PO Box 360, Blantyre 3, Malawi. flampiao@medcol.mw
Telephone: +265-1878058 Fax: +265-111872644
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Abstract

In the past decades, a lot of advances in understanding the biochemistry and physiology of the pineal gland have been made. There is evidence that it interacts with many endocrine as well as non-endocrine tissues to influence their metabolic activity modulating many organs and functions. Melatonin is secreted by the pineal gland in the brain and plays an important role in regulating the neuroendocrine system. This hormone is one of the major role players in the regulation of the circadian sleep-wake cycle. It is normally released from the pineal gland during the night in response to environmental changes in light. Studies have shown that melatonin plays a role in the regulation of many reproductive processes such as puberty, gonadal function, and pregnancy. Beside these, melatonin has been shown to be able to directly neutralize a number of free radicals and reactive oxygen and nitrogen species. The main objective of this review is to provide comprehensive information about the new developments in melatonin research regarding its role in reproduction. A review of international scientific literature was done and a question-and-answer format was used in an attempt to convey comprehensive information in a simple manner. This review discusses evidence currently available relating to the effect of melatonin on reproductive processes. It deliberates the mechanism of action of melatonin, its effect on puberty, testicular and ova function, pregnancy, and oxidative stress. A growing body of scientific evidence is suggesting that melatonin plays an important role in reproductive function. It is therefore imperative to highlight the beneficial effects of this hormone in improving the reproductive processes.

Key words: Melatonin; Reproduction; Reactive oxygen species; Antioxidants; Pineal gland

Core tip: In recent years, many studies have been focusing on the role melatonin plays in the process of reproduction. The low success rate in assisted reproductive technologies due to the detrimental effects of oxidative stress has led to studies investigating the potency of melatonin as an antioxidant. Studies have shown that melatonin reduces oxidative stress and contributes to oocyte maturation, embryo development, and luteinization of granulosa cells. Clinical studies have demonstrated that melatonin treatment for infertile women increases intra-follicular melatonin concentrations, reduces intra-follicular oxidative damage, and increases the chances of pregnancy. This review highlights the effects of melatonin in reproduction.

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INTRODUCTION

In the past few decades, a lot of studies regarding the biochemistry and physiology of a hormone called melatonin (*N*-acetyl-5-methoxytryptamine) have taken place. This hormone is secreted during the dark hours at night by the pineal gland and is responsible for the regulation of a variety of important central and peripheral actions

related to circadian rhythms and reproduction[1]. Although melatonin is primarily synthesized and secreted by the pineal gland, it is has been reported that it is also formed in tiny amounts by other organs such as the retina, harderian gland, gastrointestinal tract, lymphocytes, and the skin[2-5]. The role of melatonin in other animal species is related to seasonal reproductive cycles. In humans, melatonin secretion levels by the pineal gland can regulate the reproductive neuroendocrine axis[6]. The increase in reactive oxygen species (ROS) generation in *in vitro* fertilization (IVF) settings has been reported to negatively affect the success rate of IVF outcomes[7-9].

Melatonin has also been reported to have free radical scavenging properties[10,11] as well as stimulating several other antioxidant enzymes[12]. Can melatonin supplementation during assisted reproductive technologies increase the success rate of these procedures? Since the body is capable of producing melatonin does endogenous melatonin production or exogenous melatonin supplementation has any effect on the reproductive processes of humans and animals?

This review will provide comprehensive information about the new developments in melatonin research specifically regarding its role in the process of reproduction of both humans and animals. It will discuss the mechanism of action of melatonin, its effect on puberty, testicular and ovarian function, pregnancy, and oxidative stress.

CURRENT AVAILABLE EVIDENCE CONCERNING THE EFFECT OF MELATONIN ON THE REPRODUCTIVE PROCESS

What is the effect of melatonin on seasonal reproduction?

There is accumulation of evidence suggesting that the pattern of melatonin secretion, which is mediated by photoperiod, directly influences reproductive function. Much of the evidence has been generated from seasonally breeding mammals[13-16]. Long-day breeding animals such as rodents have been shown to be depressed during winter months (when elevated melatonin levels are at their longest nocturnal duration). The reproductive quiescent period was also prevented by surgical removal of the pineal gland[17]. On the other hand, short-day breeders such as sheep, and white-tailed deer were shown to be sexually very active and capable during the shortest days of the year, when melatonin levels are highest in terms of their nocturnal duration[18,19]. These observations suggest that melatonin is neither antigonadotrophic nor progonadotrophic. Thus, the changing duration of the nocturnal melatonin message is a passive signal that provides the hypothalamo-pituitary-gonadal (HPG)-axis information as to the time of year[20].

In a study involving male and female Syrian hamsters which were maintained under naturally occurring short days and reduced temperatures, it was observed that they developed gonadal regression. This regression was reversed by surgical removal of the pineal gland[21]. This is evidence that the reproductive axis obviously uses the seasonally dependent melatonin rhythm to adjust testicular and ovarian physiology accordingly.

Investigations using long-day and short-day breeding animals have enormously contributed to the understanding of the mechanisms whereby day length and melatonin govern seasonal reproduction. These findings have led to the successful use of melatonin as a pharmacological agent to advance the breeding season of sheep and to induce estrous cycles and increase lambing during the interval when these animals would normally be experiencing seasonal anestrus[22-24].

How does melatonin influence the selection of sexual mates?

Some studies have demonstrated that melatonin may be involved in the selection of sexual partner. It was observed that administering melatonin to male zebra finches in the drinking fluid in combination with carotenoids enhanced the brightness of the carotenoid-based pigmentation in their bills[25]. Since males with brighter coloured bills are more likely to be selected as a mate by females, melatonin may aid in the selection of a mate. Colourful plumage generally signals superior genetic quality and is common ploy used by many bird species as a sexual attractant[26].

More evidence of the role of melatonin on the selection of sexual mate has been demonstrated by the two-spotted goby fish[27]. Treating the skin explants of gobies with a combination of either melatonin and melanocyte-stimulating hormone or melatonin and prolactin, led to an exaggerated orange colouration and transparency of the belly skin. This colouration change induced by melatonin and other hormones would presumably benefit the individual in terms of attracting a sexual mate.

PINEAL MELATONIN BIOSYNTHESIS AND REGULATION

How is melatonin synthesized and regulated?

The production of melatonin by the pineal gland exhibits a circadian rhythm with low level of production during day time and high levels during the night[28,29]. During the process of melatonin synthesis, Tryptophan is hydroxylated to 5-hydroxy-tryptophan and subsequently into serotonin. Serotonin is acetylated to form *N*-acetylserotonin and then converted into melatonin (Figure 1). The suprachiasmatic nucleus (SCN) which is the major circadian oscillator that receives light input from the retina through the retino-hypothalamic tract is the one that regulate the circadian melatonin production[30]. When melatonin is formed in the pineal gland, it is not stored there, but released immediately into the blood or into the cerebrospinal fluid. It is metabolized mainly in the liver.

What is the mechanism of action of melatonin?

Melatonin exerts its actions through two types of recep-

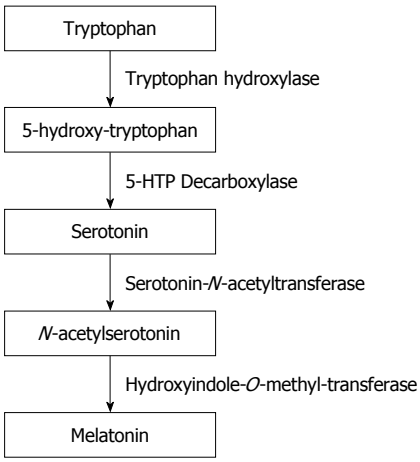

Figure 1 Biosynthesis of melatonin. 5-HTP: 5-hydroxy-tryptophan.

tors belonging to the super-family of G-protein coupled receptors. These receptors contain seven typical transmembrane domains and are called the MT_1 and MT_2[31,32]. The MT_1 and MT_2 are membrane bound receptors which are widely distributed in different organs of the body, including the brain and other peripheral organs.

When these receptors are activated they cause inhibition of adenyl cyclase activity[33] and inhibition of forskolin-induced cyclic adenosine monophosphate (cAMP) formation which result in the reduction in activated protein kinase[34]. In mammals melatonin has been reported to affect the reproductive function by activation of melatonin receptor sites within the HPG-axis[35].

Neonatal pituitary cells have been shown to express MT_1 and MT_2 subtype of melatonin receptors. These receptors when activated lead to a decrease in cAMP production and activity of protein kinase A, and attenuation of gonadotropic releasing hormone (GnRH)-induced gonadotropin secretion[36].

EFFECT OF MELATONIN ON PUBERTY

What is the effect of melatonin on the onset of puberty?

During fetal life and the first year of life, the HPG-axis is active, but becomes quiescent thereafter until around 10 years. Its reactivation depends on the progressive increase in the levels of GnRH which subsequently lead to the pulsatile secretion of luteinizing hormone (LH) and follicle stimulating hormone[37]. It has been reported that melatonin secretion has an inhibitory influence on the hypothalamic secretion of GnRH in humans[38]. It is therefore speculated that before puberty, melatonin concentrations are too high thus inhibiting the hypothalamic activation. But prior to puberty, the levels of melatonin decline below the threshold value thus forming the trigger signals of GnRH from the hypothalamus which leads to the onset of pubertal changes[39]. Therefore, it is the decline of melatonin levels that trigger puberty. Studies have demonstrated that high nocturnal melatonin secretion in children delays puberty[40] whereas low levels of melatonin have been shown to be associated with precocious puberty[41].

How does melatonin modulate sexual maturation?

The mechanism by which the HPG-axis is inhibited by melatonin after the first year of life until puberty is not well elucidated. However, there are reports that point to the influence of melatonin on the HPG-axis. These include, the evidence that melatonin is involved in the control of pulsatile secretion of LH[42] and that there is a negative correlation between nocturnal melatonin and LH concentrations[43]. Furthermore, high levels of serum melatonin in women have been shown to be associated with amenorrhea accompanied with decreased GnRH/LH pulsatile secretion[44,45]. Similarly, increases in nocturnal peak amplitude and duration of melatonin were reported in amenorrhoeic athletes who displayed irregularities in hypothalamic-pituitary-ovarian-axis functioning[46,47]. *In vitro* studies have demonstrated that melatonin leads to the down-regulation of the *GnRH* gene expression in a cell line containing GnRH secreting neurons[48].

MELATONIN AND GAMETE FUNCTION

What is the effect of melatonin on testicular function?

In animal studies, it has been shown that melatonin may modulate testicular function. In mice and rats it was reported that melatonin has an inhibitory effect on Leydig cells[49,50]. The Leydig cells are responsible for the production of testosterone. Mel_{1a} and Mel_{1b} receptor mRNAs are expressed in epithelial cells of rat epididymis suggesting that melatonin has a role in the regulation of epididymal physiology[51]. The epididymis is important for the maturation and storage of spermatozoa before they are ejaculated into the female reproductive tract.

There are contradictory reports concerning the effect of melatonin on spermatozoa function. It has been reported that long term administration of melatonin to healthy men is associated with decreased semen quality[52]. Sperm concentration, motility as well as testosterone levels were found to be significantly decreased in healthy men administered with melatonin. On the other hand, an *in vitro* study demonstrated that administration of melatonin to human spermatozoa improved progressive motility and reduced the number of static cells[53]. In another study in which melatonin levels were measured in fertile and infertile men, it was found that serum and seminal melatonin levels in infertile men were significantly reduced compared with the levels in the fertile men[54]. This demonstrated that melatonin may be involved in the modulation of the reproductive neuroendocrine axis in male infertility.

What is the effect of melatonin on ovary function?

The role of melatonin in the production of female gametes is focused on its direct actions in the ovary. It is able to pass through all cell membranes and enter all tissues because of its lipophilic property, however, it specifically concentrates in the ovary when injected systemically[55]. Studies have shown that high levels of melatonin are found in human preovulatory follicular fluid at concen-

trations which are much higher than those in serum[56,57]. It has been reported that the follicular fluid melatonin levels depend on the follicular growth[58]. The larger the follicle the higher the melatonin concentration. When oocytes are incubated in medium with melatonin supplementation during *in vitro* maturation, they have lower levels of ROS than control (without melatonin treatment) oocytes[59]. The ability of melatonin to promote embryo development in different species has correspondingly been reported. When mouse embryos were cultured in medium containing melatonin, increased blastocyst development rates were observed[60]. This suggests that melatonin may be involved in embryo development.

EFFECT OF MELATONIN ON PREGNANCY

What role does melatonin play in human pregnancy?

People living in the Arctic region have shown that their pituitary-gonadal function and conception rates are lower in the dark winter months than in the summer[61]. It has been further observed that during these dark periods of the winter season, the increases in serum melatonin concentration correlate with reduced activity of the anterior pituitary-ovarian axis[62]. The precise role of melatonin in human pregnancy is not clear. However, it has been reported that serum melatonin levels are higher during pregnancy than in nonpregnant women[63]. Moreover, twin pregnancies have been reported to yield higher nocturnal melatonin levels than singleton pregnancies[63]. This suggests that melatonin might have a role to play in human pregnancy. Clinical studies have demonstrated that melatonin treatment for infertile women increases intra-follicular melatonin concentrations, reduces intra-follicular oxidative damage and elevates fertilization and pregnancy rates[8].

Does melatonin play a role in fetal development?

Because melatonin is a small molecule, it gets transferred from the maternal circulation into that of the fetus through the placenta[64]. This means that the fetal circulation mirrors a circadian rhythm of plasma melatonin similar to that of the mother[65]. It has also been reported that there are melatonin receptors in the human fetal SCN. It is believed that melatonin is involved in the regulation of the circadian rhythm in the fetus. It has been observed that if maternal melatonin is suppressed, both *MT1* gene and clock genes are affected, suggesting that maternal melatonin has a role in modulating fetal clock gene function[66]. The generation as well as maintenance of circadian clock function depends on clock genes[67].

What is the role of melatonin in parturition?

In some mammals such as rats, parturition occurs during daytime[68]. Continuous darkness abolishes the photoperiodic timing of parturition[69]. If the pineal gland is removed in rats, the daytime delivery birth pattern is abolished and melatonin replacement therapy restores it[70]. It is well documented that the human myometrium has functional melatonin receptors[71]. Administration of melatonin has been shown to modulate the strength of affinity of gap junctions found in the myometrium[72,73]. These gap junctions serve to coordinate individual myometrial cell contractions into powerful labor inducing forces[72], thus implicating melatonin as a possible role player in the mechanism underlying the initiation of parturition.

MELATONIN AND OXIDATIVE STRESS

What are the sources of oxidative stress in the human reproductive system?

In females ROS is locally produced during the rupturing of the follicle at the time of ovulation[74]. It has been suggested that the ROS are involved in the ovulation process. There is a surge of LH during ovulation which induces dissolution of the basement membrane between the granulosa and theca internal layers and an expansion of the theca capillaries into the avascular granulosa cell layer to form a dense network of capillaries. These endothelial cell capillaries contribute to the generation of the free radicals[74]. Neutrophils and macrophages are also reported to reside in follicles[75]. These macrophages and neutrophils produce tremendous amounts of free radicals. The locally produced free radicals seems to have an important role on follicle rupture, since ROS have been shown to act as second messengers modulating the expression of genes that govern physiological processes of oocyte maturation[76,77]. However, excess ROS is responsible for oxidative stress which can damage molecules and structures of oocyte and granulosa cells within the follicle. Hence the ROS must be continuously scavenged to keep only small amounts necessary to maintain normal cell function.

In the male reproductive system, the cellular component of semen is a huge source of ROS. Morphologically abnormal and immature spermatozoa together with the presence of leukocytes can generate ROS in human ejaculates. Spermatozoa do generate ROS at the level of the plasma membrane and mitochondria[78]. Studies have shown that human spermatozoa generate superoxide (O_2^-), which spontaneously dismutates to hydrogen peroxide (H_2O_2)[79].

In the male genital tract and the ejaculate, ROS are not only derived from the spermatozoa, but can also be generated by leukocytes, which physiologically produce even up to 1000 times more ROS than spermatozoa[80,81]. This high ROS production by leukocytes plays a major role in infections, inflammation and cellular defense mechanisms. Basically, the cellular mechanisms for the generation of ROS in leukocytes and spermatozoa are the same, yet in leukocytes it is a physiological necessity to release large amounts of O_2^- into phagocytic vesicles during the killing action of pathogens.

Considering the extraordinary high content of polyunsaturated fatty acids in their membrane, the sperm plasma membrane is particularly susceptible to oxidative stress and the double bonds of the membrane lipids can

easily be oxidized by excessive ROS levels present in the sperm cells' environment. These can either be produced in large amounts by leukocytes or the spermatozoa themselves. In case of ROS attacking the plasma membrane lipids, a process called "lipid peroxidation" is initiated. Ultimately, this process decreases membrane fluidity of both plasma and organelle membranes and, as a result, damages membrane function, ion gradients, receptor-mediated signal transduction, *etc*[82]. Hence, with the loss of membrane function, spermatozoa lose the ability to function properly and therefore, fertilization is impaired[83].

Is melatonin a free radical scavenger?

Usually melatonin exerts its effects through its receptors, but it can also act directly as a powerful free radical scavenger by detoxifying the highly reactive hydroxyl radical[84,85]. There are numerous other reports confirming the scavenging abilities of melatonin on ROS and reactive nitrogen species[86,87]. Some of the free radicals scavenged by melatonin include O_2^-, H_2O_2, hydrochlorous acid, nitric oxide and the peroxynitrite anion[88-91]. The antioxidant properties of melatonin as a cell protector have been extensively studied and its scavenging ability have been reported to be higher than that of well known scavengers such as vitamin C and vitamin E[86]. Apart from scavenging free radicals directly, melatonin has a high capability to detoxify ROS and suppress its oxidative effects indirectly by enhancing the production of endogenous antioxidants. Melatonin has been shown to stimulate the scavenging activities and mRNA levels of antioxidant enzymes including superoxide dismutase, glutathione peroxidase, and catalase[92,93].

CONCLUSION

In recent years, a lot of research focused on the effect of melatonin as a direct free radical scavenger. This has greatly broadened our understanding of its multiple physiological roles. Melatonin's role in the regulation of reproductive physiology has been demonstrated in photoperiod dependent breeding mammals, and it seems to be receptor mediated mechanism in hypothalamus and pituitary gland. Currently, most of the research on melatonin is focusing on its local role as an antioxidant. The intrafollicular role of melatonin in the ovary has been demonstrated. Melatonin, secreted by the pineal gland, has been reported to be taken up into the follicular fluid from the blood. The free radicals produced within the follicles, especially during the ovulation process, are scavenged by melatonin, and reduced oxidative stress may be involved in oocyte maturation and embryo development. Evidence is pointing to the fact that melatonin treatment for infertility in women increases intra-follicular melatonin concentrations which subsequently reduces intra-follicular oxidative damage and elevates fertilization and pregnancy rates. The safety of exogenous melatonin treatment has been demonstrated in many studies[94,95]. Animal studies have also shown that melatonin has no detrimental effects on mouse and rat embryo development both *in vitro* and *in vivo*[96,97]. Future studies will indicate whether melatonin treatment could become a new cure for improving oocyte and sperm quality in infertile patients.

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MINIREVIEW

Role of bariatric surgery in the pelvic floor disorders

Christos Iavazzo

Christos Iavazzo, Iaso, Maternity Hospital, 14231 Athens, Greece
Author contributions: Iavazzo C solely contributed to this paper.
Correspondence to: Christos Iavazzo, MD, MSc, PhD, Iaso, Maternity Hospital, 38, Seizani Str., Nea Ionia, 14231 Athens, Greece. christosiavazzo@hotmail.com
Telephone: +30-694-8054119 Fax: +30-694-8054119
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Abstract

Pelvic floor disorders are very frequent among women. Weight loss can help them to achieve urinary and faecal continence again. In this narrative review, the possible mechanisms of pelvic floor disorders in obese women, their symptoms and the role of bariatric surgery in changing their quality of life are presented. We retrieved the included results of our study after performing a systematic, electronic search in PubMed (December 17, 2012) and Scopus (December 17, 2012). The main mechanism causing the development of pelvic floor disorders is chronically increased abdominal pressure as it overts structural damage or neurologic dysfunction predisposing to prolapse and incontinence. The symptoms include a sensation of vaginal fullness or pressure, uterine descent, sacral back pain with standing, vaginal spotting from ulceration of the protruding cervix or vagina, coital difficulty, lower abdominal discomfort, and voiding and defecatory difficulties. Evidence indicates that massive weight loss (45 to 50 kg) improves incontinence in morbidly obese women after bariatric surgery. Faecal incontinence is also improved after bariatric surgery. This review highlights the role of bariatric surgery in weight reduction of obese women that could act as a treatment for the pelvic floor disorders faced by those women offering improvement in incontinence as well as quality of life.

Key words: Obese women; Surgical treatment; Incontinence; Prolapse; Quality of life

Core tip: Pelvic floor disorders are very frequent among women. Weight loss can help them to achieve urinary and faecal continence again. In this narrative review, the possible mechanisms of pelvic floor disorders in obese women, their symptoms and the role of bariatric surgery in changing their quality of life are presented.

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INTRODUCTION

Overweight and obesity are defined as abnormal or excessive fat accumulation that presents a risk to health. Body mass index (BMI) is a simple index of weight-for-height that is commonly used to classify overweight and obesity in adults. It is defined as a person's weight in kilograms divided by the square of his height in meters (kg/m^2)[1]. According to the World Health Organization, obesity is classified as class I for a BMI between 30 and 34.9 kg/m^2, class II for a BMI between 35 and 39.9 kg/m^2, and class III for a BMI $\geq$ 40 kg/m^2[1,2]. Current data estimate that obesity is increasing worldwide especially in the developed countries[1,2]. A rise is also noticed in the younger population (18 to 29 years) and especially in women[2]. The impact of obesity on quality of life is broad causing even pelvic floor disorders among other conditions.

Pelvic floor disorders (urinary or faecal incontinence and pelvic organ prolapse) are common conditions affecting many obese women today. The exact prevalence of pelvic floor disorders in the general population is approximately 11%, but it should be higher in obese women[3]. In the different studies, pelvic floor disorders affect between 2% and 42% of women, depending on the definition of the condition and the study population[4-6].

The aim of this narrative review is to present the role of bariatric surgery operations in the improvement of the pelvic floor disorders that many obese women are facing, as well as the effect on the quality of life of obese women.

METHODS

Data sources

We retrieved the included results of our study after performing a systematic, electronic search in PubMed (December 17, 2012) and Scopus (December 17, 2012). Both PubMed and Scopus search strategy included the combination of the key words: (bariatric surgery or pelvic floor disorders) and incontinence and prolapse. Cochrane database (December 17, 2012) was also searched in order to look for any reviews on this argument. The reference list was also hand-searched for additional studies.

Study selection criteria

Studies reporting data on the role of bariatric surgery in pelvic floor disorders were included in this review. Abstracts in scientific conferences and studies published in languages other than English, German, French, Italian and Spanish were excluded from this review. Studies which referred to male patients were also excluded.

Results

The search performed in PubMed and Scopus retrieved a total of 11 and 14 search results, respectively, among which 10 studies (7 retrospective studies, 1 letter to the editor and 2 reviews) which were identified as eligible for inclusion in this review. No additional studies were identified through hand-searching of references.

Possible mechanisms explaining the correlation between obesity and pelvic floor disorders.

The main mechanism causing the development of pelvic floor disorders is chronically increased abdominal pressure as it overts structural damage or neurologic dysfunction predisposing to prolapse and incontinence[7-10]. Elevated abdominal and intravesical pressures are also found in patients with increased sagittal abdominal diameter and elevated BMI[1,2], while significant weight loss improves stress urinary incontinence[11,12]. Animal studies showed an association between obesity and urinary incontinence by evaluating urethral sphincter incontinence, urethral length or tone[13]. Some studies suggest that neurogenic disease caused by obesity might lead to pelvic floor disorders[11-13]. For example, a study proposed that the risk for abnormal median nerve conduction was 3.5-fold greater in obese workers, while a higher incidence of lumbar disk herniation is also found in obese patients[14,15]. Other etiologic mechanisms are either the direct injury and denervation to the pelvic floor musculature or defects in the supporting system of the endopelvic fascia and ligaments[16]. Conditions such as menopausal status, chronic constipation, chronic cough, and heavy lifting major predisposing factors[17].

Symptoms

More than 90 percent of morbidly obese women experience some degree of pelvic floor disorders, and 50 percent of these women report that symptoms adversely impact quality of their life[18]. In these women, obesity was found to be strongly correlated in predicting pelvic floor disorders in the same extent as obstetric history[18]. Although signs of pelvic organ prolapse are frequently observed, the condition seldom causes symptoms especially in younger ages[19]. However, vaginal or uterine descent at or through the introitus can become symptomatic. Symptoms may also include a sensation of vaginal fullness or pressure, sacral back pain with standing, vaginal spotting from ulceration of the protruding cervix or vagina, coital difficulty, lower abdominal discomfort, and voiding and defecatory difficulties[19]. An association between obesity and urinary incontinence exists, while the association between obesity and other pelvic floor disorders is less clear. However, Chen *et al*[20] showed the presence of any pelvic floor disorder in 75% of the obese patients compared with 44% in non-obese ($P < 0.0001$). More obese patients experienced stress urinary incontinence, urge urinary incontinence, and anal incontinence, but not pelvic organ prolapse. The severity of those symptoms were higher in more obese patients[20].

Bariatric surgery

Bariatric surgery is suggested to be the only consistently-effective long-term treatment for morbid obesity[21]. The name "Bariatric surgery" is derived from the Greek words baros and iatriki denoting respectively "heavy weight" and "medicine". In the United States, figures from 2010 indicate that the number of bariatric surgical operations carried out that year was 218000[22,23]. Bariatric surgery is associated with long-term weight loss and decreased overall mortality. It could lead to a mean weight loss of between 14% and 25% (depending on the type of procedure performed) at 10 years, and a 29% reduction in all cause mortality when compared to standard weight loss measures[24]. Bariatric surgery includes a variety of procedures and its efficacy is based on both the restriction of the quantities of ingested food (vertical banded gastroplasty, adjustable gastric band, sleeve gastrectomy, gastric balloon and the malabsorption of the nutrients through the shunted gut (biliopancreatic diversion, endoluminal sleeve)[25-35]. However, the main factor in the success of any bariatric surgery is still a strict post-surgical change of life attitude to a healthier pattern of eating. Since weight is a modifiable risk factor for incontinence, weight reduction may be an effective treatment. Studies of weight loss have examined its effects and explored the pathophysiologic mechanisms of improvement in pelvic floor disorders.

Role in urinary incontinence

A number of studies have shown improvements in urinary incontinence after bariatric surgery[8,12,36,37]. Evidence indicates that massive weight loss (45 to 50 kg) improves

incontinence in morbidly obese women after bariatric surgery[11,12]. Women who achieved a weight loss of 5%-10% or greater had at least a 50% reduction in incontinence frequency[38]. It is reported that an average weight loss of 69% of excess body weight could lead to significant changes in sagittal abdominal diameter (32 to 20 cm, $P < 0.0001$) and intravesical pressure (17 to 10 cmH_2O, $P < 0.001$)[37]. In another study, a weight loss greater than 50% leads to a reduction in stress urinary incontinence from 61% to 11.6% ($P < 0.001$)[11]. Similar studies reported improvement in urodynamic parameters after bariatric surgery operations[8,12]. Greater weight loss was associated with greater improvement of incontinence; as from the patients who lost more than 18 BMI points, 71% regained urinary continence[39].

Surgically induced weight loss has a beneficial effect on symptoms of pelvic floor disorders in morbidly obese women. In a questionnary based study, it was shown that the prevalence of pelvic floor disorders symptoms improved from 87% before surgery to 65% after surgery[40]. There was also a significant reduction in total mean distress scores after surgery, which was attributed mainly to the significant decrease in urinary symptoms. Moreover, reductions in the scores were noted for the other pelvic floor disorders, while quality of life total scores also improved. Age, parity, history of complicated delivery, percent excess body weight loss, BMI, type of weight loss procedure and presence of diabetes mellitus and hypertension had no predictive value for postoperative outcomes in the same study[40]. Cuicchi *et al*[41] evaluated clinically and instrumentally pelvic floor disorders before and after bariatric surgery in obese women and found that a clear association exists between BMI and urinary incontinence. Weight loss after bariatric surgery resulted in improved urinary incontinence, fecal incontinence, and symptoms of pelvic organ prolapse[41]. After a mean BMI reduction of 10 kg/m^2, the prevalence of pelvic floor disorders decreased to 48%, with a significant improvement in quality of life. The prevalence of urinary incontinence decreased from 61% to 9.2% and was associated with the decrease in postoperative BMI ($P = 0.04$)[41]. A recent study also showed that weight loss after bariatric surgery can result in resolution of symptoms in nearly half of women with stress urinary incontinence and three quarters of women with overactive bladder and is associated with significant improvement in quality of life[42]. On the other hand, according to McDermott *et al*[43] the prevalence of pelvic floor disorders did not improve greatly after surgery. More specifically, even with significant weight loss (BMI, 43.7 kg/m^2 to BMI, 29 kg/m^2), there was no significant difference in the prevalence of pelvic floor symptoms before and after surgery (94% to 81%, respectively) the first postoperative year. However, significant weight loss improved the degree of bother and quality of life related to these symptoms as it was shown by PFDI-20 and PFIQ-7 scores[43].

Role in faecal incontinence

The role of obesity in faecal incontinence is less well defined. The prevalence of faecal incontinence in the general population is reported to be 2% to 9%[5,44]. Obesity appears to be correlated with higher rates of faecal incontinence and diarrhoea. However, in morbidly obese patients undergoing evaluation for bariatric surgery, the prevalence of anal incontinence was notable at 32%, while incontinence of liquid stool was 21.1% and solid stool was 8.8%[45]. The effects of bariatric surgery on these conditions are not well defined. A systematic review showed that faecal incontinence improved after Roux-en-Y gastric bypass in studies with preoperative data, while the effects of bariatric surgery on diarrhoea were unclear[46]. It should be mentioned that one of the major disadvantages of the biliopancreatic diversion with duodenal switch operation is diarrhea. Although duodenal switch is associated with more bowel episodes than gastric bypass, the difference is not statistically significant. More specifically, bowel habits were found to be similar in patients who achieved 50% estimated body weight loss with duodenal switch surgery or gastric bypass[47].

Quality of life

Recently data were analyzed from 421 female patients undergoing bariatric surgery, based on a screening questionnaire ["Minnesota Multiphasic Personality Inventory, 2nd ed., Restructured Form (MMPI-2-RF)"]. The women were dichotomized as those pelvic floor disorders ($n = 121$) and those without pelvic floor disorders ($n = 300$)[48]. Women with pelvic floor disorders were found to be more psychiatrically vulnerable. More specifically, they were significantly older and more likely to evidence a history of substance abuse/dependence and depression. A trend was also found for previous inpatient hospitalization, outpatient behavioral health treatment, and psychotropic medication usage[48]. For this reason, one could understand that bariatric surgery could offer better continence control, quality of life and psychological balance.

CONCLUSION

Bariatric surgery can lead to significantly weight reduction of obese women. This method also acts as a treatment for the pelvic floor disorders that those women face by offering improvement in incontinence and quality of life.

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MINIREVIEW

Past, present and future of primary systemic treatment in breast cancer

José L Alonso-Romero, Antonio Piñero-Madrona

José L Alonso-Romero, Antonio Piñero-Madrona, Department of Oncology and Surgery, "Virgen de la Arrixaca" University Hospital, 30120 Murcia, Spain
Author contributions: Alonso-Romero JL and Piñero-Madrona A contributed to the conception, design, writing and final approval.
Correspondence to: Antonio Piñero-Madrona, MD, PhD, Department of Surgery, "Virgen de la Arrixaca" University Hospital, Ctra Madrid-Cartagena s/n, 30120 Murcia, Spain. antonio.pinero@carm.es
Telephone: +34-968-369677 Fax: +34-968-395537
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Abstract

Primary systemic treatment is a fundamental part of breast cancer therapy, and it is applied to non-surgical and locally advanced tumours as well as surgical tumours to increase the likelihood of conservative treatment. Its aim is to achieve the best possible survival with better cosmetic results and with the lowest number of treatment-related secondary effects. Before treatment is started, it is necessary to attain the best knowledge of the biological features and locoregional extension of the tumour. To do so, it is necessary to obtain a biopsy of the lesion with a wide bore needle, as well as good radiological knowledge of the disease. Therefore, currently, the use of a dynamic magnetic resonance imaging (MRI) of the breast should be included in all cases. In addition, before it is started, especially in those tumours in which conservative treatment is considered, one or several radiopaque markers should be put into place to make it possible to locate the area to be treated if there is a considerable or complete response. Systemic treatment is mainly based on combined chemotherapy with anthracyclins and taxanes, in addition to some biological agents with demonstrated efficiency for increasing the likelihood of complete disease response (trastuzumab in patients with Her-2/neu overexpression). However, there is room for neoadjuvant hormone treatment, in patients with hormone receptor overexpression, especially in those cases in which chemotherapy is contraindicated as well as in elderly patients with a relatively short life expectancy. The assessment of preoperative treatment should be based on adequate radiological tests, and nowad these should include MRI before taking decisions about adequate surgical treatment. The objective of primary treatment is to be able to increase survival and improve the chances of local treatment in the case of locally advanced treatment, achieving results that are at least equal to those of adjuvant treatment in the case of surgical tumours, but with greater chances of conservative surgery. Although the objective is survival, achieving complete pathological response seems to be a reasonable related objective, although these are more closely linked in some tumour subtypes.

Key words: Breast cancer; Breast carcinoma; Primary systemic therapy; Neoadjuvant chemotherapy; Neoadjuvant therapy

Core tip: Primary systemic treatment is a fundamental part of breast cancer therapy, and it is applied to non-surgical and locally advanced tumours as well as surgical tumours to increase the likelihood of conservative treatment. As in any kind of tumour, an attempt should be made to include these patients in clinical trials to allow us to define the best and earliest individualised treatment strategy for our patients.

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INTRODUCTION

In the specific case of breast cancer, two overriding theories of the biological behaviour of tumors in terms of their mechanisms of metastatic dissemination have predominated over the past two centuries, paving the way for two opposing paradigms: Halsted's mechanistic theory and Fisher's systemic theory. However, observations and evidence from subsequent studies have revealed that an intermediate theory, Hellman's spectrum theory, is more realistic and accounts for the differences observed in different kinds of scenarios[1].

In light of this historical background, the treatment of most malignant tumours is complex and requires interdisciplinary teams of physicians who are specialists in various fields working holistically to control them.

Therefore, breast cancer should be considered as a systemic disease in order to achieve optimal management outcomes, at least from a conceptual point of view. This should be the case even when cancer is theoretically confined to this organ (localized breast cancer) and requires local and systemic treatment for its control.

Systemic adjuvant treatment (hormone therapy, chemotherapy, immunotherapy, biological therapy against a specific molecular target), used to control micrometastatic disease after curative intent surgery, has been proven to reduce recurrence risk by 0.77 and breast cancer mortality by 0.83[2]. This benefit has been attained, although to a varying degree, regardless of axillary lymph node infiltration, the state of the hormonal receptors, the histological subtype, the level of tumour differentiation, or the expression of other predictive response factors (Her-2/neu).

However, for some patients adjuvant treatment is not the best approach and the use of neoadjuvant chemotherapy (primary or preoperative) is preferred before the local treatment of the disease.

Consequently, neoadjuvant treatment has transformed from a treatment for patients with locally advanced breast cancer (making surgery more likely in tumours in which local treatment with curative intent could not be guaranteed), into the treatment used in initially surgical tumours to enable conservative breast surgery. Taking into account that neoadjuvant and adjuvant chemotherapy provide similar benefits in terms of overall and disease-free survival in operable tumours[3], neoadjuvant treatment is currently providing a greater knowledge of the *in vivo* effects of modern treatment options in tumours prior to surgery.

PRELIMINARY TERMINOLOGICAL CONSIDERATIONS

From chemotherapy to systemic therapy

Classically, the systemic cancer treatment was based on the use of chemotherapy, that is, medication against neoplastic tissues with greater or lesser sensitivity and specificity, which directly influences the real achilles heel of this treatment: morbidity associated with the secondary effects of the toxicity of non neoplastic cells and tissues. Nowad, other modalities must be considered which are not related to classical chemotherapy. This is the situation with hormone therapy, which has a fundamental role in the specific case of breast cancer, or with the application of molecular-targeted therapies, through monoclonal antibodies, or immune tolerance induction (or suppression) therapies through vaccines or antibodies. These therapies try to increase effectiveness against different types of cancers by attempting to increase the specificity of treatment and to avoid these secondary effects.

For all of these reasons, the most appropriate term we should adopt is "systemic therapy" given that it encompasses the different therapeutic modalities, in addition to chemotherapy.

From neoadjuvancy to primary therapy

At first glance the term neoadjuvant therapy was used to refer to the fact that the therapy is administered before other treatments considered as main ones, unlike adjuvant therapy which was assigned after these treatments. Thus, a temporal relationship was explicitly established, involving an implicit subordination of importance between the treatments according to when they were applied. However, two points should be made: firstly the treatment of any type of cancer is usually multimodal, as it should be, with aspects of the treatment targeted at treating the primary tumour and others focussed more on avoiding or treating its dissemination, and which should generally be considered as having a complementary application. The second point refers to the importance of different treatment strategies used in cancer, which are determined by their effectiveness, efficacy (and even efficiency) and are not based on whether they are administered at an earlier or later stage. In this way, the sequencing of the different treatments is a secondary aspect and priority must be given to carrying out the most comprehensive treatment possible: it would be just as pointless to treat the primary tumour without worrying about the occurrence of distant dissemination as it would be to treat the disease as a whole while underestimating the primary focus of the disease thus allowing the persistence or recurrence of locoregional disease which could contribute to a potential focus of future dissemination. Therefore, it would be convenient to sideline the terms referring to the connotations of "main role" or "adjuvancy" of treatment options and to keep to those that refer to temporal sequence (primary).

HISTORY OF NEOADJUVANT CHEMOTHERAPY: THE REASON FOR PRIMARY TREATMENT

Neoadjuvant chemotherapy was first reported in breast cancer in the 1970s as an early-stage treatment for inoperable locally advanced tumours[4] and in several studies

carried out between 1980-1990 which showed an improvement in the surgery rates in these patients, as well as an improvement in their survival rate, so that it became established as part of the initial standard treatment in these patients.

As well as allowing for the surgery of these tumours that were initially non-surgical and improving the survival rate of these patients, it was found that primary chemotherapy could play a role in reducing the initial size of tumours thus making it possible to perform conservative surgery in patients in which mastectomy had initially been established as the surgical treatment. In this situation, it had to be demonstrated that primary chemotherapy was able to achieve the same effects already shown by adjuvant chemotherapy in the reduction of recurrence and overall and disease-free survival[1], and also in the improvement of the percentage of patients in which conservative surgery could be performed.

Many non-randomised studies have investigated the ability of neoadjuvant chemotherapy to increase the possibilities of conservative treatment in surgical breast cancer. Generally, the results obtained in these studies using this kind of chemotherapy achieved clinical response rates of between 67%-85%, with complete pathological responses of nearly 3% and conservative surgery rates of 85%[5-7].

Several studies have prospectively and randomly analysed phase Ⅲ trials on the use of adjuvant chemotherapy compared with the same chemotherapy administered neoadjuvantly in patients with operable breast cancer without revealing any difference in overall survival or disease free survival and achieving a significant increase in the rates of conservative surgery of breast cancer. It is worth highlighting two studies due to their design and the number of patients included: NSABP B-18[8] and EORTC 10902[9].

In the NSABP B-18[8] study, 1523 patients diagnosed with surgical breast cancer (T1-3, N0-1) were randomly administered 4 cycles of chemotherapy with adriamycin and cyclophosphamide (60-600 mg/m^2) as neoadjuvant or adjuvant chemotherapy. A clinical response was achieved in 79% of the patients treated with neoadjuvant chemotherapy, with 36% complete clinical responses and 13% complete pathological responses. What is more, 68% conservative surgeries were achieved in the neoadjuvant chemotherapy arm compared to 60% in the initial surgery arm, especially in patients with tumours greater than 5 cm in diameter.

With more than 15 years of follow-up no differences were found between both groups in terms of survival. An increase in local ipsilateral recurrence was observed in patients receiving primary chemotherapy (10.7 *vs* 7.6) especially in patients under 50 years, which was attributed to the fact that they were not treated with tamoxifen, although this absence of hormone treatment occurred equally in both treatment arms.

In addition, those patients that achieved complete pathological response had a significant improvement in terms of disease-free survival and overall survival compared to those who had residual disease after neoadjuvant chemotherapy.

In the EORTC 10902[9] study, 698 patients diagnosed with breast cancer (T1-4, N0-1) were treated with 4 cycles of 5-fluorouracil, epirubicin and cyclophosphamide (600-60-600 mg/m^2) administered adjuvantly and neoadjuvantly. The response obtained in patients treated with primary chemotherapy was 49% with 4% complete pathology responses. A 23% conservative surgery rate was achieved in patients initially programmed for mastectomy before neoadjuvant chemotherapy.

With a follow-up period of more than 4 years, there were no differences in disease-free survival, overall survival or locoregional recurrence. Significantly, the patients treated with neoadjuvant chemotherapy with complete pathological response had a significant advantage in terms of survival compared to patients with residual disease.

In 2005, Mauri *et al*[10] reported a meta-analysis of 9 randomised studies, including 3946 patients, that faced the same adjuvant and neoadjuvant systemic treatment administered for local treatment (surgery or radiotherapy). There were no differences in terms of survival [RR = 1.00 (95%CI: 0.90-1.12)], disease-free survival [RR = 0.99 (95%CI: 0.91-1.12)] or progression free survival [RR = 0.94 (95%CI: 0.83-1.06)], although there was an increased possibility of local recurrence in patients treated with neoadjuvant chemotherapy [RR = 1.22 (95%CI: 1.04-1.43)], probably because in those patients in which it was administered it was decided not perform surgery and to treat the patients exclusively with locoregional radiotherapy [RR = 1.53 (95%CI: 1.11-2.10)].

Therefore it can be concluded that neoadjuvant chemotherapy is fundamental for the primary treatment of locally advanced tumours, and that in surgical tumours it is an alternative to adjuvant chemotherapy, offering the same survival rate and a comparatively significant increase in conservative treatment rates.

CURRENT SITUATION OF PRIMARY THERAPY: CERTAINTIES AND CONTROVERSIES

Indications

The use of primary systemic therapy is currently indicated in two situations:

The initial treatment of non-surgical locally advanced tumours, before locoregional treatment: (1) for patients with locally advanced or inflammatory tumours, initial systemic treatment allows for the use of subsequent locoregional treatment, which would not have been possible in the first place, and it also provides an added improvement in survival and disease free survival. In these patients, no randomised studies have been carried out for comparing neoadjuvant and adjuvant treatment given that initial surgical treatment is impossible; and (2) in the treatment

of these patients we know that when complete pathological response is achieved there is an advantage in survival compared to when complete response is not attained[11,12].

The initial treatment of tumours in which conservative treatment is considered this should be as a more likely option than radical surgery (mastectomy). In these patients we know that there are similar survival and disease free survival rates in those treated with either neoadjuvant or adjuvant chemotherapy. This means that there is no clear disadvantage for neoadjuvant treatment in terms of locoregional recurrence when it allows for an increase in the possibilities of conservative treatment provided that it is followed by correct hormone treatment and locoregional radiotherapy if required[10].

From a theoretical viewpoint there are advantages to neoadjuvant treatment compared to the adjuvant variety: (1) the possibility of demonstrating the *in vivo* efficacy of the therapeutic agents used by assessing tumour response, offering the theoretical advantage of being able to replace those treatment options that are not useful by others which display a better antitumoral response. However, these "made to measure" treatments have shown no advantage in terms of survival or disease free survival; and (2) identifying biomarkers that allow us to obtain early information about the antitumor activity of the two treatment options would allow us to take faster decisions when we use survival as the fundamental variable.

However, the feasible use of primary systemic treatment could also have disadvantages for initial surgical treatment: It could delay the use of local curative-intent treatment in surgical tumours that could be resistant to systemic treatment. It has been confirmed that this resistance is uncommon but it accounts for around 5% in most studies[8,9,13,14]. It could lead to difficulties for carrying out a correct clinical locoregional staging prior to surgery, preventing the selection of an appropriate systemic treatment or leading to an incorrect disease prognosis being established at a later stage. Nowad, this is less important because initial systemic treatment is very homogeneous from the beginning (with the use of anthracyclines and taxanes) and is mainly based on known biological factors (*e.g.*, the use of trastuzumab/lapatinib in patients with overexpressed Her-2/neu), and additionally we can make accurate locoregional staging through the study of the sentinel node prior to neoadjuvant chemotherapy.

Selection of patients who are candidates for primary treatment

The following patients are candidates for this treatment: (1) patients diagnosed with non-surgical locally advanced breast cancer: tumours greater than 5 cm in diameter (T3), or attached to the thoracic wall (T4a), or with skin ulceration or satellite lesions (T4b), or both (T4c); axillary lymph nodes attached to each other (N2); supraclavicular lymph node involvement (N3); inflammatory tumours (T4d); (2) patients diagnosed with surgical breast cancer, to increase the chances of conservative surgery. Traditionally, a 3 cm tumour diameter has been accepted as the cut-off point although some studies have included tumours of 2 cm. From a practical point of view this treatment can be offered to all patients who have an a priori disproportion between the tumor and breast size which presupposes mastectomy or a poor cosmetic result after initial conservative treatment; (3) patients contraindicated against surgery and in whom surgery should be delayed: a recent acute myocardial infarction, a recent cerebrovascular accident, pregnancy, *et al*; and (4) fragile elderly patients in which surgery would involve too high a risk and who could benefit from initial medical treatment.

Diagnosis and staging in patients before systemic therapy

Initial diagnosis should be carried out before starting primary systemic treatment and preferably through biopsy using a wide bore needle rather than a fine needle, located either by palpation or, better still, guided by ultrasound. In addition to confirming the existence of tumor invasion, this biopsy should provide enough tissue for the study of estrogen, progesterone and Her-2/neu receptors, as well as other biological markers that could be used in other research studies.

Initial staging should make use of the TNM system, and the "c" prefix is advised in pretreatment staging and "y" in pathological staging after surgery. For the assessment of lymph node staging it is recommended to use the "c" when assessment is clinical or radiological, "f" if it included fine needle aspirations and "sn" if a study of the sentinel gland has been carried out.

All the patients should have had a thorough physical examination, at least one bilateral mammography exam, a breast ultrasound analysis, and correct systemic staging, above all in the case of locally advanced tumours to rule out distant metastasis.

LOCOREGIONAL STAGING

Assessment of the primary tumour

Before beginning primary chemotherapy a locoregional analysis should be carried out which should include a physical examination, a bilateral breast analysis, a breast ultrasound study, and in addition, the lesion should be located with a radiopaque (clip) marker which makes it possible to locate the lesion after chemotherapy in preparation for surgical treatment when there is a complete clinical response[15,16].

Magnetic resonance imaging (MRI) provides high definition anatomical images of the breast and the tumour, as well as the dynamic study of the uptake and elimination of contrast making it possible to define the existence of other tumour foci not seen using conventional analyses (multicentricity and multifocality). In addition, it allows for a better definition of possible chest wall involvement. However, although its sensitivity is greater than that of other radiological techniques, its specificity is not so sharp, so that it identifies suspicious lesions that are not malign, often leading to overtreatment.

Currently, a histological analysis is recommended (taking a biopsy with a fine or wide bore needle) of the potentially malignant lesions identified using MRI, if these findings alter the plan initially set out. These lesions could be located using guided ultrasound (second-look)[17] or otherwise using a MRI-guided biopsy, for which there are specific kits available[18].

The positioning of a radiopaque marker could be done at the time of the ultrasound-guided histological diagnosis, when the need for neoadjuvant treatment is initially considered. Alternatively, it can be done at a second stage, before beginning treatment or once it has been started and treatment response has been seen, although in the latter case it is important to closely monitor the response to avoid the disappearance of the lesion before being marked. It is particularly useful for locating the area for carrying out conservative surgical treatment if a complete clinical and radiological response is achieved, and to guide the pathologist in the search for tumor remnants and to identify microscopic disease persistence or a truly complete pathological response[1,19].

Axillary lymph node assessment

It is particularly important to carry out axillary lymph node assessment before the start of neoadjuvant chemotherapy in those patients who are surgical from the outset, although it can also be beneficial in selected cases for some patients with locally advanced disease.

Its utility is guaranteed because it allows for patient prognosis as well as the choice of chemotherapy for treatment (*e.g.*, the addition of taxanes to the anthracyclins if there is lymph node affectation).

However, this need could change in the years to come, especially if we take into account that the addition of taxanes seems to be beneficial to the adjuvant treatment of patients with negative lymph nodes. In addition, the prognostic and therapeutic assessment of the disease increasingly depends on biological factors analysed in the primary tumour rather than on classical prognostic factors such as axillary lymph node infiltration.

This assessment can be carried out through physical examination, axillary radiological examination (mainly ultrasound) and fine needle aspiration of the suspicious lesions, but clearly the best assessment is achieved through selective analysis of the sentinel node. These techniques have a sensitivity of between 70% and 90%, but this is lower where axillary involvement is due to micrometastasis.

Selective analysis of the sentinel node

It is debatable whether the sentinel node should be studied before or after chemotherapy in patients with operable breast tumours with clinically negative lymph nodes if they are going to be treated using primary systemic treatment[20].

The analysis of the sentinel node after neoadjuvant chemotherapy is made difficult by the fact that it is identified to a lower extent, probably due to structural changes in lymphatic drainage brought about by chemotherapy, and a greater percentage of false negatives due to chemotherapy response.

The potential advantages of the analysis of the sentinel node before chemotherapy include the prevention of these confusions caused by the chemotherapy itself, together with the guarantee of the appropriate choice of systemic treatment and the correct subsequent locoregional treatment after it has been completed, preventing unnecessary axillary lymph node dissections or reducing the volume of locoregional radiotherapy.

However, this procedure involves subjecting the patient to two operations and only on a few occasions will it modify the type of chemotherapy that will be received; systemic treatment usually includes anthracyclins and taxanes for achieving the best possible response and this is mainly decided upon according to the studies of biological markers in the biopsy of the primary tumour.

A systematic review of 27 studies including 2148 patients subjected to a selective biopsy of the sentinel node after chemotherapy confirmed that the lymph node was identified in 91% of patients (95%CI: 88-93) and the false negatives were 10.5% (95%CI: 8.1-13.6)[21]. This study concluded that during surgery of the primary tumour and after neoadjuvant chemotherapy, the sentinel node is a useful tool for considering post chemotherapy treatment.

Few data are available comparing the pre and post chemotherapy procedure. In a series of cases in which the first 31 were carried out after chemotherapy and a further 58 before, it was found that in 99% *vs* 87% the sentinel node was identified and there were false negative rates of 0% *vs* 16% (pre *vs* post)[22].

No data are available for comparison of the biopsy before and after neoadjuvant chemotherapy over a prolonged follow-up period making the treatment of choice a matter of opinion. While there are data that lead us to believe that this analysis is a useful tool after chemotherapy, doing it beforehand is going to bring about a more precise knowledge of the situation and will allow for maximum subsequent locoregional treatment (axillary radiotherapy).

Systemic staging

In addition to the locoregional staging (axillary and primary tumour) previously reported, before beginning treatment it is necessary to perform a correct systemic staging of the disease. As a general rule, and following the recommendations of the published guidelines, it would be enough to test surgical tumours using adequate anamnesis, a thorough physical examination, radiography of the thorax and a comprehensive medical analysis including bone and hepatic biochemical tests. Analysis with computerized axial tomography, bone scintigraphy or even positron emission tomography (PET) or PET with computed axial tomography (PET/CAT) would be performed when considered necessary due to any alterations in the previous test results.

In the case of locally advanced tumours, and given that the possibilities of distant dissemination from diag-

nosis are higher, computerized axial tomography would be indicated from the beginning, leaving bone scintigraphy and PET/CAT for those situations in which it was considered as a clinical recommendation or there were suspicious alterations in the tests previously carried out.

Choice of neoadjuvant treatment

There are many possible treatment options with neoadjuvant intent: hormone therapy, targeted therapeutic treatment, to name a few, but the treatment of choice is mostly going to be based on polychemotherapy.

Neoadjuvant hormone therapy

Most of the studies published on primary systemic treatment are based on combination chemotherapy, but recent studies with neoadjuvant hormone therapy are being reported, especially in elderly patients or in those in which for some reason the chemotherapy is considered as an unacceptable treatment option.

Most of the studies carried out are about tamoxifen, although in recent years data is becoming available on studies with aromatase inhibitors.

In 2009, Syed *et al*[23] published a study in ASCO comparing treatment with adjuvant tamoxifen after surgery or tamoxifen administered exclusively without surgery, in 1031 elderly patients with operable breast tumours. The 5-year survival rate was greater in those patients treated with surgery than in those that were only treated with tamoxifen (95% *vs* 85%) in patients between 70 and 80 years of age, but survival was the same in those over 80 years (90% for both), and it was concluded that in these patients with a short life expectancy exclusive administration of tamoxifen could prevent surgical treatment.

Few data are available comparing hormone therapy with neoadjuvant chemotherapy.

A randomized phase Ⅱ study compared 3 mo treatment with exemestane or anastrozol with 4 cycles of chemotherapy with adriamycin and paclitaxel in 121 postmenopausal patients with positive hormone receptors. There were no differences in median time until response (57 d *vs* 51 d), complete pathological response (3% *vs* 6%) or clinical response (67% and 62% in exemestane and anastrozol *vs* 63% in chemotherapy). No differences were found regarding conservative breast surgery (33% *vs* 24%) or locoregional recurrences (3.3% *vs* 3.4%)[24].

No differences were found in either premenoupausal patients in complete response or clinical response or in type of surgery when faced with exemestane and goserelin treatment with 4 cycles of epirubicin-cyclophosphamide followed by 4 cycles of docetaxel[25].

In general and with the data available until now it could be said that the preference for neoadjuvant chemotherapy over hormone therapy is reserved for patients in which chemotherapy is not indicated and in which surgery is not the only initial option (patients with locally advanced or surgical tumours contraindicated for surgery and chemotherapy).

Hormone treatment is an alternative to surgery in tumours in elderly patients with a relatively short life expectancy.

Among the hormone treatments available, the treatment of choice is aromatase inhibitors rather than tamoxifen, given that there are data showing that the responses are more frequent and the possibilities of conservative treatment are higher, although it is not clear that this will lead to an increase in survival[26-29].

It is also unclear how long treatment should last, but in the absence of progression, most studies suggest between 3-4 mo, and it would seem to be reasonable to continue until month 6 or more if there is a response before surgery, to later complete 5 years of adjuvant treatment.

Primary chemotherapy

As we have already seen, neoadjuvant chemotherapy achieves the same overall and disease free survival as the same schemes administered adjuvantly, with an increase in the possibilities of conservative breast surgery. However, there are data pointing towards an increased possibility of local relapse, although they are not conclusive.

The treatment of choice is based on the principle that the chemotherapy that is efficient in adjuvant treatment has a similar efficacy in neoadjuvant treatment, and therefore there is no reason to use different schemes.

In locally advanced non-surgical tumours and those surgical ones in which an increase in conservative surgery is sought after, obtaining a maximal response is a reasonable objective, and this is achieved by combining anthracyclins and taxanes[30-34], whether simultaneously or sequentially (Table 1).

It is generally recommended to administer all the planned chemotherapy before the surgical procedure, if there is no evidence of progression, to maximse clinical response or complete pathological response.

In those patients contraindicated for the use of anthracyclins the exclusive use of taxanes or the combination with capecitabine or vinorelbine could be a valid option.

It is not clear whether the schemes with increased dose density (the same dose of chemotherapy in shorter periods of time) could improve the data of the conventional schemes. Along these lines, the GerparDuo study randomized 913 patients with T1-3N0-2 breast cancer in 4 cycles of chemotherapy with adriamycin and docetaxel every 14 d and compared them with 4 cycles of AC every 21 d followed by 4 cycles of docetaxel every 21 d. The data were favourable for sequential treatment (in other words, with a lower dose density) with greater pathological responses and a higher level of conservative surgery[35].

There are data supporting the use of dose-dense treatments especially in patients with negative hormone receptors, given that in a published meta-analysis, these treatments, used adjuvantly or neoadjuvantly, could be associated with better overall and disease free survival

Table 1 Chemotherapy schemes used in neoadjuvant treatment, with category-1 evidence and that can be used in neoadjuvant treatment

Ref.		Chemotherapy scheme	Drugs/dose
Martin *et al*[70]		CAT	Docetaxel 75 mg/m^2 *iv* on day 1 Doxorubicin 50 mg/m^2 *iv* on day 1 Cyclophosphamide 500 mg/m^2 *iv* on day 1 Cycled every 21 d for 6 cycles (all cycles are with filgrastim support)
Citron *et al*[71]	Non-trastuzumab containing regimens	Dose-dense AC followed by paclitaxel every 2 wk	Doxorubicin 60 mg/m^2 *iv* on day 1 Cyclophosphamide 600 mg/m^2 *iv* on day 1 Cycled every 14 d for 4 cycles Followed by paclitaxel 175 mg/m^2 as a 3 h *iv* infusion on day 1 Cycled every 14 d for 4 cycles (all cycles are with filgrastim support)
Henderson *et al*[72]		AC followed by weekly paclitaxel	Doxorubicin 60 mg/m^2 on day 1 Cyclophosphamide 600 mg/m^2 *iv* on day 1 Cycled every 21 d for 4 cycles Followed by paclitaxel 80 mg/m^2 as a 1 h *iv* infusion weekly from day 1 for 12 wk
Jones *et al*[73]		CT	Docetaxel 75 mg/m^2 on day 1 Cyclophosphamide 600 mg/m^2 *iv* on day 1 Cycled every 21 d for 4 cycles (all cycles are with filgrastim support)
Romond *et al*[74]	Trastuzumab containing regimens	AC followed by weekly paclitaxel concurrent with trastuzumab	Doxorubicin 60 mg/m^2 *iv* on day 1 Cyclophosphamide 600 mg/m^2 *iv* on day 1 Cycled every 21 d for 4 cycles Followed by Paclitaxel 80 mg/m^2 as a 1 h *iv* weekly for 12 wk With Trastuzumab 4 mg/kg *iv* with first dose of paclitaxel Followed by Trastuzumab 2 mg/kg *iv* weekly to complete 1 yr of treatment Cardiac monitoring at baseline, 3, 6, and 9 mo
Robert *et al*[75]		TCH	Docetaxel 75 mg/m^2 *iv* day 1 Carboplatin AUC 6 *iv* on day 1 Cycled every 21 d for 6 cycles With Trastuzumab 4 mg/kg in week 1 Followed by Trastuzumab 2 mg/kg for 17 wk Followed by Trastuzumab 6 mg/kg *iv* every 3 wk to complete 1 yr of trastuzumab therapy Cardiac monitoring at baseline, at 3, 6, and 9 mo

CAT: Docetaxel, doxorubicin and cyclophosfamide; AC: Doxorubicin plus cyclophosfamide; CT: Docetaxel plus cyclophosfamide; TCH: Docetaxel, cyclophosfamide plus trastuzumab.

rates[36]. However, it would be necessary to gather data from well-designed phase Ⅲ studies to consider dose-dense treatments as a standard treatment.

Positive Her-2/neu tumors

The addition of trastuzumab to patients with an overexpression of Her-2/neu has demonstrated a survival benefit both in the context of adjuvant therapy as well as in advanced disease.

In the same way, the use of trastuzumab is recommended in the neoadjuvant treatment of Her-2/neu positive patients given that it increases the possibility of complete responses. There are phase Ⅲ studies comparing the addition of trastuzumab to neoadjuvant chemotherapy (NOAH[37], GeparQuattro[38]). In both cases the addition of trastuzumab significantly increases the chances of a complete pathological response (43% and 31.7% compared to 23% and 15.7% respectively), without any changes in the survival rate or percentage of patients treated with conservative surgery.

A meta-analysis has been carried out comparing the addition of trastuzumab to schemes without it, including 5 studies with 515 patients and the conclusion is similar to the previous one: a significant increase in the chances of achieving a complete pathological response without adding toxicity or changing the likelihood of carrying out conservative treatment[39].

Lapatinib, a biological drug with anti thyrosin-kinase activity, achieves results that are similar to those of trastuzumab when it is used in an isolated way and associated with chemotherapy, according to the results reported in ASCO in 2012. Both drugs achieve similar complete response rates, regardless of the status of the hormone receptors. However, the addition of them does not increase the percentage of pathological responses[40].

The results of the Neo-ALTTO study, however, contradict the previous results, showing that the addition of trastuzumab and lapatinib to neoadjuvant paclitaxel significantly increases the percentage of complete pathological response (51.3% in combined treatment compared with 29.5% and 24.9% with trastuzumab and lapatinib as single treatments, respectively)[41], although with greater toxicity.

The addition of pertuzumab, another anti-Her2/neu antibody, to trastuzumab and docetaxel as a neoadjuvant treatment significantly increases the chances of pathological responses by nearly 45.8% (according to the results of a randomized phase Ⅱ study), compared to trastuzumab and docetaxel on their own[42].

The use of any of these drugs is still not recommend-

ed (lapatinib or pertuzumab) as a standard treatment with neoadjuvant intent.

Triple negative tumours

Although many studies suggest that the percentage of complete pathological response is greater in triple negative patients than in the rest, it remains unclear whether this produces some kind of benefit in these patients. In fact, in spite of the increase in complete response these patients still have a poor prognosis with lower expectations in terms of survival.

There are no specific defined treatment schemes for these patients although there are data suggesting promising results using derivates from platinum[43] PARP inhibitors (especially in patients with the BRCAs mutation) and antiEGFR1 drugs.

The current recommendations are to use the same treatments that are used for the rest of the patients, although this is undoubtedly a fertile area for specific clinical trials which are likely to change the treatment used in the near future.

Other biological treatments

The addition of bevacizumab (an anti VEGF antibody, with mainly antiangiogenic activity) to chemotherapy in negative Her-2/neu patients has revealed contradictory results. In the GeparQuinto[44] study, with 1948 patients, bevacizumab was able to increase the percentage of complete pathological responses in triple negative patients but not in patients with an overexpression of hormone receptors. However, the NSABP B-40 study[45] on 1206 patients achieved the opposite effect, producing an increase in pathological responses in patients with an overexpression of hormone receptors but not in triple negative patients.

Therefore, until more substantial results are obtained, its use is not recommended in this context.

Tailoring

In spite of the advantage of neoadjuvant treatment for checking the *in vivo* sensitivity of certain drugs (so that a change in the chemotherapy scheme could provide advantages in the case of progressive disease or limited response), this benefit has not been demonstrated in the only phase Ⅲ study carried out with this objective.

In the GeparTrio[46] study on 2070 patients treated using the CAT scheme (cyclophosphamide, doxorubicin and docetaxel), those who do not achieve a response of at least a 50% reduction in tumour size are randomized to continue with CAT or to receive treatment with vinorelbine and capecitabine, and do not achieve any differences in response according to ultrasound tests, complete pathological responses or percentage breast conservation.

Another one of the issues to be taken into account within systemic treatment tailoring is to know if it makes sense to prolong this treatment once surgery has been performed and a partial response has been achieved, whether this is a result of the initial treatment or of an alternative type of treatment.

It might be thought that systemic treatment is not the most appropriate strategy and further treatment or another kind of treatment could increase efficacy, or alternatively, that the limited response or the lack of response to the systemic treatment is a reflection of the fact that we are facing a tumour with a worse prognosis which is therefore less chemosensitive.

Until now, no study has demonstrated that the administration of any kind of systemic treatment after standard preoperative treatment improves the prognosis of these patients.

Outside of a clinical trial no recommendation has been made for additional systemic treatment following surgery, after standard preoperative treatment.

Assessment of treatment response

The assessment of treatment response involves the assessment of clinical response as much as pathological response after surgery. Both prognostic factors are related to survival.

It is vital to carry out an exhaustive clinical follow up during systemic treatment because although a change in systemic chemotherapy in the absence of treatment response has not proven to be useful[36], clinical disease progression or the absence of response is enough to postpone systemic treatment and to consider immediate adequate locoregional treatment.

The clinical and radiological response should be made according to the RECIST criteria[47,48], so that a bidimensional assessment of the lesions can be made. Complete clinical response can be defined as the disappearance of the tumour in both the breast and the axillary lymph node through physical examination and radiological tests.

The traditional methods for examining the breast (physical examination, mammogram and ultrasound) have a limited ability to assess response and are not very closely correlated with pathological response[49].

However, dynamic MRI has been better correlated with pathological response in many studies and in one meta-analysis[50]. In spite of its increased sensitivity compared to other techniques it has more false positives and overestimates the occurrence of residual disease after systemic treatment[51].

By carrying out early dynamic MRI after initiating chemotherapy it is possible to distinguish respondent patients (in whom there is an early-onset decrease in contrast enhancement compared to levels in previous tests), from non-respondents, in whom this enhancement is maintained or increased[52].

MRI can also underestimate the result of chemotherapy revealing residual disease or disease which is very unresponsive to treatment, and this seems to be especially related to the use of taxanes in the chemotherapy regimes'[53].

Although MRI can provide underestimations or overestimations of response to chemotherapy, currently it is undoubtedly the radiological method of choice for assessing neoadjuvant treatment response.

In those patients studied given MRI after systemic treatment, the possibility of overestimating the disease should be assessed before planning surgical treatment given that conservative surgery would become less likely in patients who could potentially receive this kind of surgery[54].

Pathological response

Although complete clinical response (disappearance of the tumour in the physical examination and radiological tests) and complete pathological response (the absence of a viable invasive tumour, depending on the accepted definition in the surgical sample) have been related with disease prognosis, there is no clear correlation between them, and approximately a third or more of the patients with complete clinical response have a viable tumour in the surgical sample[55].

In most of the initially reported studies, a significant reduction in tumour size was achieved making conservative treatment more likely, but this had no correlation with disease-free or overall survival.

Achieving complete pathological response is a very important surrogate marker for determining the efficacy of preoperative treatment and it has been correlated in several studies and a recent meta-analysis[56] with better results in disease survival and it is considered as a marker of systemic disease chemosensitivity.

The definition of complete pathological response varies among the reported studies. In some studies complete response has been considered as the absence of tumour cells in the primary tumour area and in the axillary node areas, whereas in other studies where it has been argued that the existence of a ductal tumour does not affect disease-free or overall survival[57], it is defined as the persistence of a non-invasive tumour. Some studies go further separating complete response in the primary tumour and in the axillary lymph node.

Although there is disagreement over complete response in the literature, it is currently thought that obtaining complete pathological response is a predictive factor, independent of disease-free and overall survival in the multivariate analysis[7].

Furthermore, the persistence of residual disease in the lymph nodes is a factor of worse prognosis than disease persistence in the primary tumour[58].

The likelihood of achieving complete response varies according to tumour biology, so that tumours with Her-2/neu overexpression and negative receptors can achieve up to a 45% chance of complete response (defined as an absence of tumour invasion) compared to those that have hormone overexpression but no Her-2/neu receptors in whom only 9% attain a complete response[59] (without trastuzumab).

In addition, complete pathological response capacity or long term survival prognosis also appears to depend on the tumour subtype, so that, complete response is the best predictor of disease-free survival especially in patients with positive hormone receptors[46].

Predictive response factors

Several predictive response factors related to achieving complete response have been reported, and therefore they are related to chemosensitivity, but they are currently still not recommended for selecting individualised systemic treatment.

We know that tumours that do not express hormone receptors or only express a few of them such as luminal B subtype and tumours with a high percentage of Ki67 expression according to immunohistochemistry, are associated with greater chances of complete pathological response to chemotherapy, while those tumours that overexpress hormone receptors or lobular histologies are less likely to achieve complete pathological response with chemotherapy[60,61].

Alternatively, Her-2/neu overexpression is a clear predictive factor of response to trastuzumab, although we also know that it increases the chances of response to inhibitors of aromatase compared to tamoxifen, when endocrine treatment is chosen[62].

The genetic profile can predict pathological results, so that it is more likely for pathological response to occur in triple negative tumours or in those who have a luminal B profile[63-65].

A recent meta-analysis concluded that complete response with chemotherapy is more likely in patients with triple negative (31.1%) and positive Her-2/neu (38.9%) tumours than in tumours that only overexpress hormone recpetors (8.3%)[66].

However, it is not just biological factors that are related with tumour chemosensitivity. Dynamic analysis, spectroscopic analysis with MRI[67], and positron emission tomography[68] can predict sensitivity to treatment if they are carried out early-on once systemic treatment has been undertaken. The differences regarding the baseline studies of contrast uptake or SUV (in the case of PET) are related with the chances of systemic treatment response.

PET has a high sensitivity for evaluating neoadjuvant treatment response but with a low specificity, so that it cannot be recommended as an isolated technique for taking decisions[69].

FUTURE OF PRIMARY SYSTEMIC THERAPY

Neoadjuvant treatment is undoubtedly a realistic option in many scenarios, but it continues to be a treatment that has potential for development, with the introduction of new treatments or new indications or even as a substitute for surgery in certain patient subgroups.

In spite of the importance of local treatment in breast cancer, over time the aggressiveness of surgery has been diminishing, making procedures more and more conservative, with less aggression against the axillary lymph node, improved cosmetic results and a reduction in secondary effects. This has all been possible thanks to the increase in the anti-tumour efficacy of systemic treatments.

Much research still needs to be done and improve-

ments need to be made to the systemic treatment of localised breast cancer with neoadjuvant intent, but in the near future, the main improvement will be the availability of an individualised treatment, based on the patient's genetic profile and predictive biological response factors, using early response assessment methods that are probably based on sufficiently sensitive image techniques and with few false positives.

An appropriate selection of systemic treatment, with local efficacy, and an adequate response assessment using imaging methods with false negatives could mean that in the future, in some patients, surgery could become unnecessary for treating localized breast cancer.

The current extensive biological knowledge about tumours is making it possible to use highly selective treatment options efficient for certain types of tumour (anti Her-2/neu drugs, for example). However, just as it has been shown in other tumours (melanoma, colon cancer, lung cancer…) shortly we will have very efficient systemic treatments for small groups of patients that could be easily selected for this purpose.

Currently many studies are in progress on a range of agents (PARP inhibitors and other targeted agents) in the neoadjuvant context.

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CASE REPORT

Prenatal incarceration of caput succedaneum: A case report

Atsuko Okazaki, Ken Miyazaki, Kana Kihira, Madoka Furuhashi

Atsuko Okazaki, Ken Miyazaki, Kana Kihira, Madoka Furuhashi, Department of Obstetrics and Gynecology, Japanese Red Cross Nagoya Daiichi Hospital, Nagoya 453-8511, Japan
Author contributions: All authors participated equally in the preparation of this case report by contributing their expertise; Furuhashi M designed and performed the research; Okazaki A provided patient's data; Okazaki A, Miyazaki K, Kihira K and Furuhashi M managed the patient with PPROM; Furuhashi M wrote the manuscript; all authors approved the final manuscript.
Correspondence to: Madoka Furuhashi, MD, PhD, Department of Obstetrics and Gynecology, Japanese Red Cross Nagoya Daiichi Hospital, 3-35 Michishita-cho, Nakamura-ku, Nagoya 453-8511, Japan. furuhashi-f@syd.odn.ne.jp
Telephone: +81-52-4815111 Fax: +81-52-4827733
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Abstract

Caput succedaneum is relatively common at birth but infrequently diagnosed in utero. We report the first case of a prenatal incarcerated caput succedaneum after cervical cerclage in a patient with premature rupture of the membranes (PPROM). A 41-year-old woman was referred and admitted to our hospital due to PPROM at 19 wk of gestation. Aggressive therapy, including amnioinfusion, cervical cerclage, and administration of antibiotics and tocolysis, was initiated. At 24 wk of gestation, a thumb tip-sized and polyp-like mass, which was irreducible, was delineated with a vaginal examination, vaginal speculum, and transvaginal ultrasonography, leading to the diagnosis of incarcerated caput succedaneum. Under general anesthesia, the incarcerated caput succedaneum was repositioned with fingers after cutting the string to avoid necrosis, and then, placement of a McDonald cervical cerclage was undertaken again. At 26 wk of gestation, she delivered a 678 g girl through an emergency cesarean section performed due to profuse bleeding and prolonged decelerations. A slight bulge with hair was observed on the head by palpation at birth. Cephalic ultrasonography, X-ray, magnetic resonance imaging and electroencephalogram confirmed no abnormality. Although the baby needed oxygen (0.2 L/min) at the time of hospital discharge, she has grown favorably at three years of corrected age.

Key words: Caput succedaneum; Cervical cerclage; Patient with premature rupture of the membranes; Ultrasonography; Prenatal

Core tip: Caput succedaneum is relatively common at birth but infrequently diagnosed in utero. Furthermore, no case of incarceration of antenatal caput succedaneum has been reported in the literature. This is the first report of prenatal and incarcerated caput succedaneum after cervical cerclage in a patient with premature rupture of the membranes (PPROM). The presenting case makes obstetricians recognize that cerclage placement, especially in a patient with PPROM, may result in unusual caput succedaneum in utero. When it develops to incarceration, earlier release should be considered to prevent the serious complication of necrosis.

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INTRODUCTION

Caput succedaneum is a cranial subcutaneous serohematic extravasation that can be differentiated from cephalhematoma by findings of extension over a suture line and definite palpable edges. It is more likely to form during a prolonged or difficult delivery and often resolves in several d without sequelae. Furthermore, it is relatively common at birth but infrequently diagnosed in utero[1-4]. We present a case of caput succedaneum that was diagnosed

by ultrasonographic examination during the antepartum period.

CASE REPORT

A 41-year-old woman, gravida 3, para 0, was referred and admitted to our hospital due to patient with premature rupture of the membranes (PPROM) at 19 wk and 6 d of gestation. Her surgical history was unremarkable, except for conization of the cervix at age 37 for carcinoma *in situ*. She had been on insulin therapy due to diabetes mellitus. On admission, she was afebrile. The plasma level of C-reactive protein (CRP) and white blood cell count were 0.1 mg/dL and 9500/mm^3, respectively. These findings showed that there was no clinical chorioamnionitis. Vaginal examination demonstrated 2 cm-dilated cervical os and amniotic fluid flowing out. Laboratory culture of the vaginal discharge was negative. She reported a history of intermittent staining since the first trimester of pregnancy. Ultrasound showed that the cervical length was 28 mm, and the maximum cord-free amniotic pocket was 2.5 cm. Although we informed her that she might have a bad prognosis, she wanted to continue the pregnancy. A catheter was transabdominally indwelled in the amniotic cavity after introduction of a 21-gauge needle under continuous ultrasound guidance. Although the amniotic culture was negative, the amniotic fluid polymorphonuclear neutrophil leukocyte, glucose, lactate dehydrogenase, and neutrophil elastase levels were 371 cells/mm^3, 20 mg/dL, 2575 IU/L, and 14.7 μg/mL, respectively, showing intraamniotic inflammation[5]. She underwent placement of a McDonald cervical cerclage using polyester tape under intravenous anesthesia to prevent cervical dilation. Subsequently, amnioinfusion was initiated, whose purpose was not retention of the fluid but lavage throuth perfusion. Approximately 1000 mL/d sterile and warm saline was spontaneously drip- infused into the amniotic cavity, and the corresponding volume of fluid flowed out every day. Magnesium sulfate and ritodrine were used for tocolysis. Antibiotic therapy was also given. Cefmetazole sodium (2 g/d *iv*), piperacillin sodium (4 g/d *iv*), anhydrous ceftriaxone sodium (2 g/d *iv*), and meropenem trihydrate (1 g/d *iv*) were administered in sequential order until delivery. The level of blood CRP and white blood cell was in the normal range. At 23 wk and 3 d of gestation, a small amount of outflow was unexpectedly observed, although a certain level of amniotic fluid was observed in utero by ultrasonography. The latter finding suggested obstruction of the cervical canal. Thus, saline inflow was kept at the level of outflow to prevent hydramnios. At 24 wk and 0 d of gestation, a thumb tip-sized and polyp-like mass, which was irreducible, was delineated with a vaginal examination. A vaginal speculum demonstrated a purple-black-colored mass with hair on the surface. These findings along with transvaginal ultrasonography (Figure 1A) led to the diagnosis of caput succedaneum. Because the most feared sequela was necrosis, we decided that the incarceration should be released. Under general anesthesia,

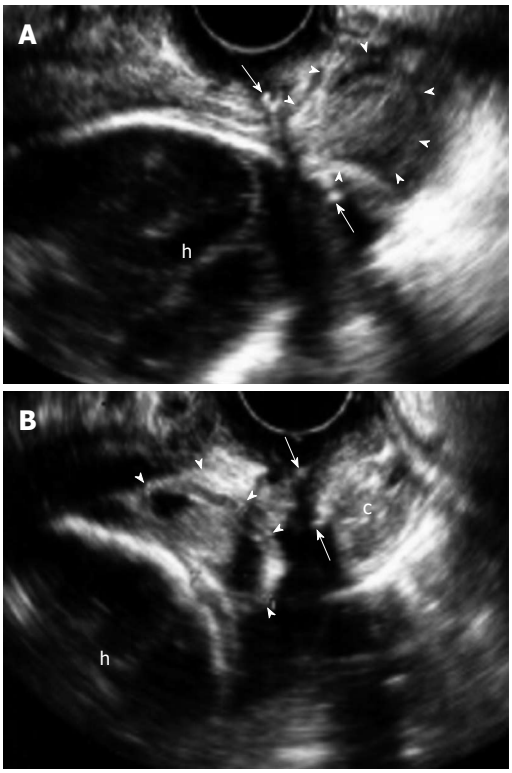

Figure 1 Transvaginal ultrasonography. A: A bulge (arrowheads) with an echogenic core was identified outside the cervical string (arrows); B: The bulge (arrowheads) was observed within the contour of the fetal head but inside the cervical string (arrows) 7 d after re-operation. h: Fetal head; c: Cervix.

the incarcerated caput succedaneum was repositioned with fingers after cutting the string, and then, placement of a McDonald cervical cerclage was undertaken again. The same treatment strategy as before was taken to allow the fetus to become mature enough to survive. At 25 wk and 0 d of gestation, transvaginal ultrasonography showed an echogenic bulge within the soft tissue of the fetal head (Figure 1B). The estimated fetal weight was 598 g, corresponding to the weight for 23 wk and 3 d. At 26 wk and 1 d of gestation, profuse bleeding occurred, and prolonged decelerations were observed on fetal heart rate monitoring. Thus, an emergency cesarean section was performed, and she delivered a 678 g girl with an Apgar score of 1 (5-min). There was a true knot of the umbilical cord. Placental pathology demonstrated histologic chorioamnionitis (Grade 3) and funisitis (Grade 2). The arterial blood gas analyses of the umbilical cord showed that the pH and base deficit were 7.04 and 17.9 mmol/L, respectively. Resuscitation was started without delay. The levels of CRP and immunoglobulin M were 5 μg/dL and 9 mg/dL, respectively. Arterial blood culture was negative. The head of the newborn baby looked normal with hair by inspection, but a slight bulge was observed by palpation at birth. Cephalic ultrasonography, X-ray, and magnetic resonance imaging confirmed no abnormality, such as an intracranial hemorrhage, a skull fracture, or a bone defect. She had a normal electroencephalogram at 1 and 40 wk after birth. The newborn central hearing

screening showed no abnormality. Meanwhile, she was affected with retinopathy of prematurity and received laser coagulation. She has grown favorably without alopecia and shows normal physical and neurological development at three years of corrected age.

DISCUSSION

The common management in most centers of PPROM before 22 wk of gestation is termination of the pregnancy or the expectant approach because expectant management results in an increased rate of fetal and neonatal morbidity and mortality[6,7]. When a patient with previable PPROM desires continuation of the pregnancy, more aggressive interventions, such as amnioinfusion[8], cervical cerclage, and intra-amniotic gelatin sponge[9], are not infrequently required in addition to the administration of antibiotics and tocolysis to prolong pregnancy until the fetus becomes viable. In such cases, our usual protocol is to supply continuous amnioinfusion, cervical cerclage, and the use of antibiotics and tocolysis after obtaining informed consent[10]. The aggressive intervention of previable PPROM results in a high neonatal survival rate[10].

Caput succedaneum is a cranial subcutaneous serohematic extravasation that is more likely to form during a prolonged or difficult delivery and often resolves in several d without sequelae. Although it has been infrequently diagnosed in utero[1-4], no case of incarceration has been reported in the literature. It would appear that several factors are associated with incarceration of caput succedaneum. Uterine contractions are primarily inevitable, as usual caput succedaneum is formed during delivery. In addition, PPROM might play a pivotal role because pressure is directly placed on the fetal scalp contiguous to the internal os of the uterus in the setting of oligohydramnios. This assumption is supported by the fact that a percentage of cephalhematoma and caput succedaneum in utero is involved in PPROM[2-4]. Cerclage placement is also a contributing factor. Even a successful cerclage may result in limited dilation of the cervix when uterine contractions are persistent because they may promote cervical maturation and diminish its thickness. In that event, the opening encircled by the suture might induce prolapse of the caput succedaneum and form an incarceration when it swells. Considering that only a slight bulge of the newborn head was observed at birth in our case, caput succedaneum in utero could spontaneously reduce but for incarceration.

One of the serious sequelae of perinatal scalp injury is halo scalp ring, which is annular scalp alopecia. Although it is usually a temporary defect, a necrotic caput succedaneum may result in scarring alopecia because deep ulceration can destroy hair follicles[11,12]. This concept suggests that incarceration of caput succedaneum is harmful to the fetus. Because it is not difficult to diagnose prenatal incarceration of caput succedaneum through vaginal examination and ultrasonography, special attention should be paid to prevent undesirable necrosis.

In conclusion, obstetricians should recognize that cerclage placement, especially in a patient with PPROM, may result in unusual caput succedaneum in utero. When it develops to incarceration, earlier release should be considered to prevent the serious complication of necrosis.

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6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

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9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

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programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer, 2002: 182-191

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15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

Patent (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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