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REVIEW

Association between gamete source, exposure and preeclampsia: A review of literature

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Abstract

Preeclampsia complicates 3%-5% of pregnancies and is one of the major causes of maternal morbidity and mortality. The pathologic mechanisms are well described but despite decades of research, the exact etiology of preeclampsia remains poorly understood. For years it was believed that the etiology of preeclampsia was the result of maternal factors, but recent evidence suggests that preeclampsia may be a couple specific disease where the interplay between both female and male factors plays an important role. Recent studies have suggested a complex etiologic mechanism that includes genetic imprinting, immune maladaptation, placental ischemia and generalized endothelial dysfunction. The immunological hypothesis suggests exaggerated maternal response against fetal antigens. While the role of maternal exposure to new paternal antigens in the development of preeclampsia was the initial focus of research in this area, studies examining pregnancy outcomes in pregnancies from donor oocytes provide intriguingly similar findings. The pregnancies that resulted from male or female donor gametes or donor embryos bring new insight into the role of immune response to new antigens in pathogenesis of preeclampsia. The primary goal of the current review is the role of exposure to new gametes on the development of preeclampsia. The objective was therefore to provide a review of current literature on the role of cohabitation length, semen exposure and gamete source in development of preeclampsia.

Key words: Preeclampsia; Donor embryos; Donor oocytes; Donor sperm; Primipaternity

Core tip: Preeclampsia is a potentially life threatening complication of pregnancy, etiology remains unresolved. For decades it was believed to be a disease of mainly maternal origin with many pathologic mechanisms being described, however evidence suggests that an interplay between maternal and paternal factors may play an important role in pathogenesis. The aim on this publication therefore was to provide review of current literature on association of gamete source, exposure and the risk of preeclampsia.

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INTRODUCTION

Preeclampsia complicates 3%-5% of pregnancies and is one of the major causes of maternal morbidity and mortality in both developed and low income countries[1]. While the physical manifestations of preeclampsia have been well characterized and may include hypertension, proteinuria and intrauterine growth restriction, the primary etiology remains unknown[1-3]. The pathologic

mechanisms described include impaired cytotrophoblast invasion of spiral arteries, exaggerated inflammatory response and endothelial cell damage with subsequent impairment of multiple organs[3,4].

Despite decades of research, the exact etiology of preeclampsia remains unclear with several proposed hypotheses that include genetic imprinting, immune maladaptation, placental ischemia and generalized endothelial dysfunction[5]. The immunological hypothesis suggests that an exaggerated maternal response against fetal antigens precipitates the pathological findings[6]. Evidence for this hypothesis stems in part from studies examining duration exposure to paternal antigens and a correspondingly lower incidence of preeclampsia in subsequent pregnancies[7,8].

Studies focused on the outcomes of pregnancies from donor oocytes confirmed the observations of initial research examining the role of maternal exposure to new fetal antigens in the development of preeclampsia. The studies on pregnancies that resulted from donor gametes (or either male or female origin) or donor embryos bring new insight into the role of immune response to new antigens in pathogenesis of preeclampsia[9-12]. The immunologic hypothesis explaining the etiology of preeclampsia is complex and beyond the scope of this article. Experimental studies shown presence of major and minor histocompatibility antigens in human semen, it is therefore seminal priming prior to pregnancy can induce maternal tolerance to paternal alloantigens and thus protect from preeclampsia[13]. These experiments focus on the expression of transplantation antigens [human leukocyte antigen (HLA)] by human trophoblast and their potential to induce maternal immunologic responses where regulatory T cells and cellular signals indolamine 2,3-dioxygenase, and transforming growth factor-β play important roles. Autoimmune mechanisms have also been with emphasis on the role of maternal antiphospholipid antibodies and anti-angiotensin Ⅱ type I receptors[14-17]. For interested readers we recommend the more comprehensive reviews of immunology and preeclampsia[17,18].

The objective of this paper is to provide a review of current literature on the role of cohabitation length, semen exposure and gamete source in development of preeclampsia.

PRIMIPATERNITY AND NULLIPARITY

The risk of preeclampsia among nulligravid women is three times higher then for multiparous women and a history of prior normal pregnancy has long been considered "protective" for the risk of preeclampsia[3,19]. The incidence of preeclampsia was higher for nulliparas in their first pregnancy, than it was subsequent pregnancies in the same women with a subsequent pregnancy, provided that it was fathered by the same partner (OR = 2.96, 95%CI: 1.80-4.88)[8].

It was thought that, in contrast to multiparas whose subsequent pregnancy is fathered by the same man, the risk of recurrence remains as high for woman with interval partner change as it is for nulliparas. These findings prompted researchers to investigate the role of a new father (or "primipaternity" a term first introduced by Robillard *et al*[20] in 1993) rather then nulliparity in the development of preeclampsia[21-23]. Subsequent investigations by Robillard *et al*[20], reviewing cases in a Caribbean population showed increased risks of preeclampsia in multiparous women after changes in paternity. Similarly, Tubbergen *et al*[24] showed prevalence of having severe preeclampsia or HELLP syndrome to be significantly higher among multiparous women who conceived with new partner. Li *et al*[25] in a large retrospective cohort study showed that change in paternity increased the risk of hypertensive disorders of pregnancy for women who were normotensive during their previous pregnancy. The results presented by Trupin *et al*[26] also support immunological hypothesis of preeclampsia. They showed that 29% of preeclampsia cases in multiparous women with an interval partner change were attributable to primipaternity, however the risk of preeclampsia remained lower in these women comparing to nulliparae. These findings imply that any previous pregnancy, even after change of partner may provide some protection. The association between preeclampsia and primipaternity was further confirmed by Bandoli *et al*[27] in the study on risk factors for preeclampsia and small for gestational age fetuses. The investigators evaluated the number of potential confounding factors, including maternal diseases, alcohol and tobacco use, history of preeclampsia and race and found that primipaternity remained a significant risk factor for preeclampsia (Table 1).

Some of the discrepancies in studies looking at new male partners may also relate to the duration of sexual cohabitation with a new partner, or duration of antigenic exposure preceding a pregnancy. Verwoerd *et al*[28] found that primipaternity was not a significant risk factor for preeclampsia. However, analysis of their results in the light of duration of sexual cohabitation, suggested that a duration of sexual cohabitation of 6 mo or fewer months was associated with increased risk of preeclampsia in multigravid group (OR = 3.9, 95%CI: 1.2-13.4). A recent prospective study by Chigbu *et al*[29] in southern Nigeria population also showed that woman who changed their partners before next pregnancy did not have increased risk for preeclampsia. In contrast to the first study investigators did not find any difference in duration of sexual cohabitation (7.9 ± 1.3 mo *vs* 7.5 ± 2.1 mo, $P = 0.531$) between women with preeclamptic and uncomplicated pregnancies. This latter study is limited by the fact that there were only 11 patients with change in paternity, which may explain the conflicting findings (Table 1).

Further evidence to support a hypotheses of immune tolerance and the documented protective effects of pregnancy, stems from the observation that women with history of miscarriage like multiparas have reduced risk of preeclampsia. Saftlas *et al*[30] evaluated 4589 nulliparous woman enrolled in Calcium for Preeclampsia Prevention

Table 1 Studies reporting preeclampsia and pregnancy-induced hypertension in relation to change of paternity

Ref.	Design	Sample size	Main outcome measures	Findings
Robillard *et al*[20]	Case control	74 hypertensive cases 60 controls	Change of paternity	Change of paternity was 61.7%, 10% and 16.6% inn PIH group, chronic hypertension group and controls respectively ($P < 0.0001$)
Feeney *et al*[21]	Matched case control	47 cases with preeclampsia 47 normotensive controls	Change of paternity	13 cases with paternity change *vs* 3 controls with paternity change ($P < 0.01$)
Ikedife[22]	Case series	46 eclamptic multiparous patients	74% of subjects had paternity change	
Chng[23]	Case report	Case of severe preeclampsia in the patient with prior history of uneventful first pregnancy after change of paternity		
Tubbergen *et al*[24]	Retrospective case control study	333 multiparous subjects with hypertensive disorder 182 multiparous normotensive subjects	Change of paternity	22.6%-preeclamptic multiparas with change of paternity; 27.0%-HELLP multiparas with change of paternity; 3.3%-change of paternity among normotensive multiparas OR for preeclampsia among subjects with new partner was 8.6 (95%CI: 3.1-23.5) and for HELLP 10.9 (95%CI: 3.7-32.3) comparing to normotensive subjects
Li *et al*[25]	Retrospective cohort	140147 pregnancies	Incidence of preeclampsia/eclampsia	OR for preeclampsia among women with previous normal pregnancy and change of paternity was 1.3 (95%CI: 1.1-1.6)
Trupin *et al*[26]	Prospective cohort	5800 pregnancies	Incidence of preeclampsia	Adjusted OR for preeclampsia among multiparas with change of paternity 1.4 (95%CI: 0.8-2.4)
Bandoli *et al*[27]	Prospective cohort	1396 pregnancies	Incidence of preeclampsia	OR for preeclampsia 2.75 (95%CI: 1.33-5.68) among women with change paternity
Verwoerd *et al*[28]	Case control	60 multigravidae with preeclampsia 60 normotensive multigravidae	Change of paternity	Change of paternity was 38.3% *vs* 21.7% (cases *vs* controls) Uncorrected OR for preeclampsia with primipaternity 2.3 (95%CI: 0.9-5.5)
Chigbu *et al*[29]	Prospective cohort	732 pregnancies	Incidence of preeclampsia	Preeclampsia in 3.5% of cases *vs* 3.1% controls (NS)
Saftlas *et al*[30]	Retrospective cohort	4589 pregnancies	Incidence of PIH and preeclampsia	Adjusted OR for preeclampsia among women with history of abortion who conceived again with same partner 0.55 (95%CI: 0.21-0.97)
Olayemi *et al*[31]	Prospective cohort	2630	Incidence of hypertension in pregnancy	History of same paternity abortion was protective against preeclampsia (HR = 0.46, 95%CI: 0.22-0.96)

PIH: Pregnancy induced hypertension; NS: Non significant.

trial and found that prior abortion fathered by the same partner reduced the risk of preeclampsia by 50%. These results were replicated by Olayemi *et al*[31] as well as Eras *et al*[32] who evaluated the risk associated with preeclampsia and found that women with an aborted pregnancy of the same paternity experienced the same protective effect against preeclampsia (Table 1).

DONATED GAMETES

Pregnancies that result from donor gametes provide another controlled opportunity to study immunologic aspects of preeclampsia. Need *et al*[33] in 1983 were the first to suggest a higher incidence of preeclampsia in pregnancies resulting from insemination with donor sperm. Although their study was an uncontrolled descriptive case series, further studies demonstrated a similarly increased risk of preeclampsia in the pregnancies that result from donor inseminations[34-36]. A retrospective study by Hall *et al*[37] however, failed to demonstrate increased risk of preeclampsia in donor sperm recipients. Although no differences were observed, the control group in this study had a higher baseline incidence of preeclampsia (11.5%) than is typically reported in the general population, perhaps accounting for the inability to detect an increased risk in the donor sperm cohort (Table 2).

Given the increased risk seen with donor sperm, one would similarly expect that pregnancies in donor oocyte or donor embryo recipients would be associated with similar risk of preeclampsia. Initial studies using an assisted reproductive technology model looking at women receiving embryos derived from donor oocytes would have similarly increased risks of preeclampsia. Studies demonstrated an increased risk to that seen in some donor sperm and primipaternity cases[10,11,38]. Although these findings were intriguing, the patients using donor oocytes were older than their controls. Klatsky *et al*[9] provided the largest in a retrospective cohort study of 158 pregnancies including aged matched controls and found an increased risk of both preeclampsia and pregnancy induced hypertension in donor oocyte recipients (OR = 4.0, 95%CI: 1.5-13.8; OR = 4.2, 95%CI: 1.5-11.9 respectively). These findings were recently confirmed again by Tranquilli *et al*[12] (Table 2).

Of note a small study of 26 donor embryo recipients failed to detect a difference, but was likely underpow-

Table 2 Studies reporting preeclampsia and pregnancy-induced hypertension in donor oocytes, donor sperm and donor embryos pregnancies

Ref.	Design	Sample size	Main outcome measures	Findings
Donor oocytes				
Söderström-Anttila *et al*[11]	Retrospective cohort	51 oocyte donation pregnancies 97 IVF age matched controls	The incidence of PIH and preeclampsia	The incidence of PIH in primiparae was 30% in oocyte donor recipients and 13% in IVF controls ($P < 0.05$), no difference in preeclampsia incidence between two groups
Salha *et al*[10]	Retrospective cohort	27 donor oocytes pregnancies 27 age-and parity matched controls	The incidence of preeclampsia	Preeclampsia incidence 16% *vs* 3.7% (cases *vs* controls), $P < 0.05$
Keegan *et al*[38]	Retrospective anonymous questionnaire study	199 oocyte donor recipients 488 autologous IVF controls	The incidence of PIH	Rate of pregnancy induced hypertension in < 35 years old was 42% *vs* 12%, $P < 0.001$ (cases *vs* controls) and > 40 years old 26% *vs* 14%, $P = 0.003$ (cases *vs* controls)
Klatsky *et al*[9]	Retrospective matched cohort	77 donor oocytes recipients 81 autologous IVF controls	The incidence of PIH and preeclampsia	16.9% of cases with preeclampsia *vs* 4.9% controls 24.7% of cases with PIH *vs* 7.4 % controls Adjusted OR for preeclampsia with donor oocytes OR = 4.0 (95%CI: 1.2-13.8) and for gestational hypertension OR = 4.2 (95%CI: 1.5-11.9)
Tranquilli *et al*[12]	Retrospective matched cohort	26 donor oocytes recipients 52 autologous ICSI pregnancies 52 AMA controls	Prevalence of preeclampsia	Prevalence of preeclampsia 19.2% in donor oocyte recipients *vs* 0% in autologous ICSI and AMA controls ($P < 0.001$)
Donor sperm				
Need *et al*[33]	Case series	584 AID pregnancies	The incidence of preeclampsia	Preeclampsia incidence 9.3%
Smith *et al*[35]	Retrospective cohort	37 donor insemination pregnancies 44 controls	The incidence of preeclampsia	24.3% of cases with preeclampsia *vs* 6.8% controls RR for preeclampsia with donor insemination RR = 1.85 (95%CI: 1.20-2.85)
Hoy *et al*[34]	Retrospective cohort	1552 donor insemination pregnancies 7717 controls	The incidence of preeclampsia	8.4% of cases with preeclampsia *vs* 5.2 % controls Adjusted OR for preeclampsia with donor insemination OR = 1.4 (95%CI: 1.2-1.8)
Salha *et al*[10]	Retrospective cohort	33 donor sperm pregnancies 33 age-and parity matched controls	The incidence of preeclampsia	Preeclampsia incidence 18.2% *vs* 0% (cases *vs* controls), $P < 0.05$
Hall *et al*[37]	Retrospective cohort	45 donor insemination pregnancies 173 controls	The incidence of proteinuric hypertension	No difference in incidence of proteinuric hypertension between cases and controls (13.3% *vs* 11.0%)
Kyrou *et al*[36]	Retrospective cohort	438 donor insemination pregnancies 275 partner sperm	The incidence of preeclampsia	Preeclampsia incidence 10.9% *vs* 7.2% (cases *vs* controls), difference 3.7%; 95%CI: -0.8 to 7.8
Donor embryos				
Porreco *et al*[39]	Retrospective cohort	23 donor embryos pregnancies 24 age matched IVF controls	The incidence of preeclampsia	26% of cases with preeclampsia *vs* 29% controls OR for preeclampsia with donor embryos OR = 0.86 (95%CI: 0.24-3.09)
Salha *et al*[10]	Retrospective cohort	12 donor embryos pregnancies 12 age-and parity matched controls	The incidence of preeclampsia	Preeclampsia incidence 25% *vs* 0% (cases *vs* controls), NS

AMA: Advanced maternal age; AID: Artificial donor insemination; IVF: *In vitro* fertilization; ICSI: Intracytoplasmic sperm injection; PIH: Pregnancy induced hypertension; NS: Non significant.

ered[39]. Pregnancies that result from surgically obtained sperm for *in vitro* fertilization (IVF) are similar, immunologically to donor sperm pregnancies, as their partners have not had sufficient antigenic exposure to their husband's sperm. In these cases maternal exposure to paternal sperm antigens prior to embryo transfer is limited, a situation that could be of a key importance if the sperm antigens, not semen antigens were responsible for mounting immunologic tolerance. Wang *et al*[40] evaluated the outcomes of pregnancies that resulted from regular IVF or intracytoplasmic sperm injection (ICSI) cycles with ICSI pregnancies were surgically obtained sperm was used. They observed that risk for pregnancy induced hypertension was doubled (OR = 2.1, 95%CI: 1.30-3.62) and risk for preeclampsia tripled (OR = 3.10, 95%CI: 1.59-6.73) in the latter group (Table 2).

LENGTH OF SEXUAL COHABITATION

Marti *et al*[41] observed that woman with preeclampsia had

Table 3 Studies reporting preeclampsia and pregnancy-induced hypertension in relation to length of sexual cohabitation and use of barrier contraception

Ref.	Design	Sample size	Main outcome measures	Results
Robillard *et al*[7]	Retrospective cohort	1011 pregnancies	Incidence of PIH	Incidence of PIH was 10.6% (entire cohort) and 5.1% among women with > 12 mo of sexual cohabitation (11.9% and 3.3% for primigravidae, respectively)
Verwoerd *et al*[28]	Case control	60 cases with preeclampsia 60 normotensive controls	Length of sexual cohabitation	Unprotected sexual cohabitation of > 6 mo was a negative predictor for preeclampsia (coefficient -0.57, SE 0.62, $P = 0.03$)
Olayemi *et al*[31]	Prospective cohort	2630 pregnancies	Incidence of hypertension in pregnancy	Length of sexual cohabitation before pregnancy was protective against hypertension in pregnancy (HR = 0.96, 95%CI: 0.93-0.99) but not preeclampsia (HR = 1.07, 95%CI: 0.00-1.15)
Kho *et al*[42]	Prospective cohort	2507 pregnancies	Incidence of preeclampsia	OR for preeclampsia were 2.32 (95%CI: 1.03-5.25) and 1.88 (95%CI: 1.05-3.36) for short sexual relationship of less then 3 mo and less then 6 mo respectively
Klonoff-Cohen *et al*[43] 1989	Case control	110 preeclamptic cases 115 normotensive controls	Contraceptive and reproductive history of subjects	OR for preeclampsia for barrier contraceptive users was 2.37 (95%CI: 1.01-5.58)
Mills *et al*[44]	Merge data from two prospective cohort studies	13914 pregnancies (total)	Incidence of preeclampsia	OR for preeclampsia in barrier contraceptive users were 0.85 (95%CI: 0.71-1.12) (one study) and 0.85 (95%CI: 0.49-1.45) (second study)
Saftlas *et al*[46]	Case control	258 cases 182 controls	Length of sexual cohabitation	OR for preeclampsia among women with long (> 90%) sexual relation-OR = 0.3 (95%CI: 0.1-0.9)

PIH: Pregnancy induced hypertension.

three times shorter length of sexual cohabitation with their partners than did women with normal pregnancies and thus proposed that spermatozoal HLA can either induce maternal tolerance to conceptus or cause maternal immunologic enhancement. The inverse relationship between length of sexual cohabitation and pregnancy induced hypertension was later demonstrated by Robillard *et al*[7]. They interviewed 1011 woman regarding paternity and length of cohabitation and found that a duration of sexual cohabitation of greater that 12 mo prior to pregnancy decreased the incidence of pregnancy induced hypertension from 10.6% to 5.1%, and that difference was even more pronounced in the primigravidae subgroup (11.9% to 3.3%). Another study documented a protective effect after only 6 mo[28] (Table 3).

Two large prospective cohort studies showed that women diagnosed with preeclampsia and gestational hypertension were more likely to have history of recent initiation of sexual relations with their partners than woman with uncomplicated pregnancies[31,42]. The short duration of sperm exposure prior to pregnancy has been postulated to be a factor responsible for higher prevalence of preeclampsia in younger populations (Table 3).

Other studies have shown that the use of barrier contraception and thereby limiting the exposure to paternal sperm antigens was associated with an increased risk of preeclampsia. Such a association was first documented by Klonoff-Cohen *et al*[43] in a case control study. Authors showed that women who used barrier contraception were over twice as likely to develop preeclampsia. These results however could not be reproduced in later study by Mills *et al*[44] in 1991 (Table 3).

The role of semen exposure and its effect on development of preeclampsia has been subject of many studies. It seems that not only duration of sperm exposure plays role. It has been hypothesized that vaginal and oral sperm exposure prior to pregnancy may exert different effects.

Vaginal exposure is not the only posited mechanism for immunologic exposure. Koelman *et al*[45] showed in a small study (41 preeclamptic patient, 44 controls) that women with preeclampsia were less likely to have been engaged in oral sex with their partners prior to index pregnancy. In their study preeclamptic women were also less likely to swallow sperm during oral sex with the father of their pregnancy. Using enzyme-linked immunosorbent assay they were able to detect soluble HLA in seminal plasma and showed that its levels were not different between men that fathered normal and preeclamptic pregnancy. The investigators postulated that oral exposure in particular, through exposure of maternal gastrointestinal tract mucous membranes to paternal soluble HLA induced a tolerance to future pregnancies with the same partner. The Koleman study, however, did not control for length of sexual relation before pregnancy. A similar case-control study of 440 pregnancies, examined the association between seminal fluid exposures and the development of preeclampsia, using detailed questionnaires about sexual practices, failed to find an association with reduced rates of preeclampsia. Increasing vaginal exposure to paternal semen, however, was significantly associated with a lower incidence of preeclampsia, with 70% reduction rate for women with the highest 10th percentile exposure[46].

CONCLUSION

Preeclampsia is a syndrome that involves both multiple organs and is associated with many risk factors. Currently,

both experimental and clinical studies support a role for immune dysfunction in the etiology of preeclampsia. We reviewed the evidence that gamete source and prior exposure may be associated with the risk of preeclampsia. Non-autologous gametes, both donor oocytes and donor sperm, as well as exposure to new paternaly derived antigens appear to play an important role in development of the disease. Most studies support the hypothesis that maternal exposure to male antigens either in sperm or through prior pregnancies has some protective effect. Available data support hypothesis that incidence of preeclampsia and pregnancy induced hypertension decrease with increasing length of sexual cohabitation. Examination of the pregnancy outcomes resulting from assisted reproduction using donor gametes contribute clinical evidence to evaluate the hypothesis that preeclampsia may be causally related to novel antigenic exposure in the conceptus.

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REVIEW

Prevention of shoulder dystocia related birth injuries: Myths and facts

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Abstract

Traditionally, brachial plexus damage was attributed to excessive traction applied on the fetal head at delivery. Recently, it was proposed that most injuries occur spontaneously *in utero*. The author has studied the mechanism of neurological birth injuries based on 338 actual cases with special attention to (1) fetal macrosomia; (2) maternal diabetes; and (3) methods of delivery. There was a high coincidence between use of traction and brachial plexus injuries. Instrumental extractions increased the risk exponentially. Erb's palsy following cesarean section was exceedingly rare. These facts imply that spontaneous neurological injury *in utero* is extremely rare phenomenon. Literary reports show that shoulder dystocia and its associated injuries increased in the United States several-fold since the introduction of active management of delivery in the 1970's. Such a dramatic change in a stable population is unlikely to be caused by incidental spontaneous events unrelated to external factors. The cited investigations indicate that brachial plexus damage typically is traction related. The traditional technique which precludes traction is the optimal method for avoiding arrest of the shoulders and its associated neurological birth injuries. Effective prevention also requires meticulous prenatal care and elective abdominal delivery of macrosomic fetuses in carefully selected cases.

Key words: Shoulder dystocia; Erb's palsy; Fetal macrosomia; Brachial plexus injury; Two-step delivery; Birth injury

Core tip: Traditionally, brachial plexus injury at birth has been considered traction related. Recently, several authors proposed that one-half or more of these injuries occur spontaneously "*in utero*" resulting from myometrial activity. Study of 338 birth injuries found close association with deliveries that had involved manual and instrumental extractions. Only one Erb's palsy occurred following cesarean section. These findings indicate that spontaneous intrauterine brachial plexus damage is extremely rare. Meticulous antenatal care, elective abdominal delivery of grossly macrosomic fetuses and non-interference with the natural birthing process are recommended for preventing shoulder dystocia and its dire consequences.

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INTRODUCTION

Since the 19th century double blind, controlled, prospective investigation has been the hallmark of scientific pedantry. However, not all medical puzzles yield themselves for evaluation by this important but costly and time consuming research approach. Injuries associated with arrest of the shoulders of the fetus at birth are eminent examples. Untold numbers of neonates are left with neurological damage following this complication every year, yet in any single service its incidence is low. Many newborn babies would need to be sacrificed at the altar

of pure science if investigators insisted on resolving this problem through this revered gold standard of research. Not since the Aztecs had offered the hearts of forty-thousand slaves to their gods have human lives been considered freely expendable for causes that contemporary society found noble and worthwhile.

Medical history shows that sophisticated methodology, whatever valuable is no substitute for intuition and deductive logic. The latter qualities made it possible for open minded scientists, such as Jenner, Lind, Holmes, Semmelweis, Pasteur, Koch, Sanger, M and P Curie, Fleming, Gregg, McBride, Friedman, Clarke and others to promote the progress of medicine. Rigid demand for experimental evidence delayed for four decades clinical implementation of "asepsis" for the prevention of childbed fever at the cost of tens if not hundreds of thousands of lives.

Not unlike in ancient Egypt, physicians face court action in the United States if their treatment entails bad outcome. Mercifully, monetary compensation has replaced death penalty that had been favored in the valley of the Nile 3000 years ago. As a result, medical documentation of incidents of birth injuries that are scattered in hundreds of hospitals can be found in abundance in the files of malpractice attorneys and insurance companies. The author's group gained access to these sources and collected 338 medical records which described shoulder dystocia related fetal injuries or deaths in detail. As explained in previous publications[1,2], in many cases the attorney's preliminary review was not followed by litigation. In those instances when court action ensued the records were only attached to the data base after the legal proceedings had been concluded. Eventually, cases were collected on the ground of the following criteria: (1) Neonatal brachial plexus damage that persisted for at least 6 mo with or without clinical diagnosis of shoulder dystocia; (2) Damage-other than brachial plexus palsy-that persisted at least six months with clinical diagnosis of arrest of the shoulders at birth; and (3) Perinatal death against the background of documented shoulder dystocia at birth.

The diagnosis of shoulder dystocia was mentioned in over 90% of the records. The remaining ones only referred to brachial plexus injury. Absence of documented diagnosis is considered by some investigators evidence to indicate that the brachial plexus palsy occurred without arrest of the shoulders[3]. This distinction is only relevant in the medico-legal context, since the injury has never been attributed to the arrest of the shoulders but to traction used by the physician or midwife in charge. Therefore, for the purpose of their studies the participants of this research included those cases in their material where brachial plexus injury occurred but the diagnosis of shoulder dystocia was not documented.

DEFINITION OF SHOULDER DYSTOCIA

Paradoxically, this important clinical complication has no generally accepted criteria. According to current American interpretation the diagnosis is applicable when in the absence of spontaneous expulsion of the fetus the "standard delivery procedure of gentle downward traction" of the fetal head fails to accomplish delivery. This definition ignores the fact that routine use of traction is disapproved in some European countries[4,5] and was discouraged in the United States also until the mid-1970's[6-9]. Non-interference with the birthing process is still practiced by British obstetricians[4,10], whose proverbial "cold blooded" detachment much impressed this writer during the years of his training in England. It has also been favored in the Perinatal Center of the UMDNJ in Newark throughout the last 40 years[11] in spite of the contrary advice of standard textbooks and of the American College of Obstetricians and Gynecologists (ACOG). By traditional interpretation interruption of the delivery process following expulsion of the fetal head is a physiological phenomenon which does not warrant intervention. It occurs at least in one-half of the deliveries of primiparous women and in about one-fourth of all multiparas. The next uterine contraction which seldom is delayed more than 2-3 min expels the body of the child spontaneously. The time interval can be shortened by administering slow intravenous infusion of oxytocin in low concentration.

Conservative interpretation of normal birthing process affects the criteria of shoulder dystocia since only when the next contraction fails to expel the body becomes this definition applicable. Therefore, with this technique the diagnosis is objective and does not depend on the judgment of the accoucheur. It is a matter of note that in the practices of physicians who embrace this approach the incidence of shoulder dystocia tends to be low[12,13].

Interpretation of the so called "turtle sign" differs for those who accept the conservative concept of shoulder dystocia from that of others. Retraction of the head from the perineum following relaxation of the uterus is considered a physiological phenomenon which requires no intervention. The fetal body is likely to be delivered spontaneously with the next contraction. It is true however, that "real" shoulder dystocia relatively often is preceded by turtle sign. It should be regarded therefore a warning about possible forthcoming arrest of the shoulders rather than a diagnostic sign of it. Most importantly, its occurrence should be considered a relative contraindication for any attempt at delivery before the next uterine contraction.

There has been some dispute about the question of whether even a short waiting for the spontaneous expulsion the fetal body is warranted before the use of traction[14]. For reason to be discussed later, the idea of prompt traction reflects unawareness of the normal mechanism of the birthing process. Because the author considers any interference at this stage of the delivery ill-advised, this subject is outside the scope of discussion at this point.

FETAL EFFECTS OF ARREST OF THE SHOULDERS

In the absence of consensus about the diagnostic criteria

Table 1 Predisposing factors for shoulder dystocia

Preconceptional	Prenatal	Intrapartum
Small maternal stature	Low glucose tolerance	Protracted latent phase
Obesity	Preeclampsia	Protracted labor (1st stage)
Diabetes (or family history)	Gestational diabetes	Protracted labor (2nd stage)
High maternal birth weight	Large for gestational age fetus	Conduction anesthesia
Past birth of LGA child	Excessive weight gain (> 18 kg)	Use of oxytocin
Narrow pelvis	Postdatism	Arrest of labor
Past incidence of shoulder dystocia	Postmaturity	Vacuum extraction
"Elderly" primigravida	Induction of labor	Forceps delivery

LGA: Large for gestational age.

of arrest of the shoulders the rate of fetal damage associated with it cannot be determined. In the Perinatal Center in Newark head and body have been delivered during separate uterine contractions in about 1 out of 3 instances. Such cases were described in the records as normal spontaneous vaginal births. Obviously, some of these deliveries would have been labeled as shoulder dystocia elsewhere. Thus, the statistics of those doctors who "pull" routinely differ from those who "do not pull". Like apples and oranges, the results of these groups cannot be compared. Therefore, the impression deriving from the literature, namely that about 1 out of 10 cases of shoulder dystocia entails lasting fetal damage is an educated guess at best.

The characteristic damages associated with arrest of the shoulders are Erb's and-less often-Klumpke's palsies. Neurologists generally endorse the opinion that these are traction related injuries[15]. Rarely, the lesion may be bilateral. Fractures of the scull, clavicle and humerus are relatively frequent and so are intracranial hemorrhage and hypoxic brain damage[16]. The latter ones can be life threatening and may occur with or without brachial plexus affliction. Injuries of the spinal cord and the phrenic nerve are rare. Minor brachial plexus lesions that are apparent at birth usually disappear after a few weeks or months. These are probably pressure rather than traction related injuries. Afflictions that persevere for more than six months are likely to remain permanent.

PREDISPOSING FACTORS FOR ARREST OF THE SHOULDERS

Factors listed in Table 1 have been found conducive to arrest of the shoulders at delivery. Because their significance varies on a broad range, only those considered of major clinical importance require discussion in some detail.

Pelvic contraction

The importance of feto-pelvic relations is obvious even for the uninitiated. The expediency that a large head cannot pass through a small opening was already taken into account by medieval architects when they built the dungeons of Castel Sant' Angelo in Rome, the Bastille in Paris and the Tower of London. Manufacturers of kings' crowns and men's hats used this knowledge even earlier. Unfortunately, physicians failed to take notice of this information until the 17th century. Consequently, "midwifery" practiced by granny midwives only turned into "obstetrics" after Mauriceau[17] had recognized the importance of the relationship between the size of the fetal head and the capacity of the mother's pelvis. Considering this background and the information that even a low for gestational age infant may encounter severe shoulder dystocia in case the pelvis is inadequate[18], the fact that some current texts describe not only antepartum but even intrapartum pelvic assessment unnecessary represents a romantic and adventurous but ill-conceived return to the Middle Ages. Also surprising is the fact that in spite of the well-recognized role of diabetes in the causation of fetal macrosomia, shoulder dystocia and other serious complications, antenatal diabetic screening in the absence of predisposing factors was still labeled unnecessary relatively recently[19].

Obesity

It is a widespread misconception that danger of postoperative complications makes abdominal delivery in morbidly obese women undesirable. Since their risks increase when cesarean section is performed after protracted labor and also because arrest of the shoulders may be as much as 10-times more frequent in this group than in the general population, gross obesity frequently makes cesarean delivery the preferable choice[20]. While reviewing cases of arrest of the shoulders at delivery it became apparent that far too often little attention had been paid to maternal weight increase during pregnancy. Insofar as obesity is conducive to diabetes and thus to excessive fetal size, the importance of preventing undue maternal weight gain by restricting its gestational increase to 10-12 kg with appropriate diet is readily apparent.

Past history of shoulder dystocia

Previous shoulder dystocia is widely considered an indication for cesarean section. While a desirable choice in most instances, trial of labor may be a reasonable alternative when predisposing factors that prevailed in the preceding pregnancy (such as gestational diabetes, fetal macrosomia, protracted labor and difficult forceps extraction)

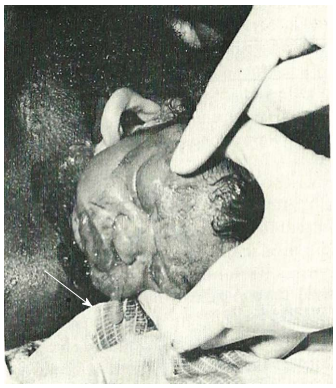

Figure 1 The picture illustrates a "2-step delivery" complicated by umbilical cord around the fetal neck. External rotation occurred shortly after the expulsion of the head and the delivery process stopped at that point. The cord was loosened but no attempt was made to extract the body. The picture taken at the onset of the next uterine contraction depicts its effect, namely expulsion of amniotic fluid from the respiratory tract (arrow). Since external electronic monitoring had demonstrated variable fetal heart rate decelerations at the end of the 2nd stage of labor, the cord complication was anticipated. Courtesy of Dr. Vivic Johnson.

are not present or appear avoidable.

Conduct of delivery

Interference with the physiological birthing process has been so widespread in recent decades that probably few obstetricians have witnessed a normal spontaneous labor and delivery during their career. In the course of its passage through the pelvic inlet the sagittal suture of the skull is in or close to the transverse diameter. As the head enters the mid-pelvis the caput rotates 90 degrees. In 96% of the instances the small fontanel moves anteriorly. It is under the symphysis when the caput reaches the outlet. These turns and the descent itself are brought about by uterine contractions and represent passive accommodation to the available space. After the emergence of the head expulsion of the fetal body is preceded by another 90 degree rotation around its axis, since the chest cannot pass between the sciatic spines unless the shoulders occupy the antero-posterior diameter of the pelvis. This process brings about "external rotation of the head" on the maternal perineum. In a considerable minority of deliveries the contraction stops after the emergence of the head but before its external rotation. It only occurs 2-3 min later. This process called "2-step delivery"[11] is a physiological phenomenon and carries no inherent risk[4-13,21-23]. Evidence of fetal compromise on electronic monitoring rarely justifies extraction of the body since the associated stress exacerbates preexisting hypoxia and may lead to meconium aspiration. Use of traction before external rotation of the head is futile and stressful for the fetus because the shoulders cannot traverse the pelvis in transverse rotation. It follows therefore that traction immediately after the delivery of the head invites arrest of the shoulders and may lead to Erb's palsy. For this reason, apart from major degree of abruption of the placenta or uterine rupture almost no situation calls for manual traction within the 3-4 min time frame of spontaneous vaginal delivery.

Tight umbilical cord around the fetal neck should be slackened but the temptation to extract the fetus must be resisted. While delivering the body the uterus compresses the chest and expels amniotic fluid and meconium from the respiratory tree (Figure 1). Cutting the nuchal umbilical cord prior to delivery of the shoulders is a dangerous polypragmasy which has no place in obstetrical practice[22,24].

In medicine as much as in everyday life to prevent a mishap one must know what brings it about. With regard to prevention of brachial plexus injuries, for reasons that go beyond the boundaries of medical science this question has become a battle ground of conflicting opinions: (1) Almost one-half of obstetrical malpractice claims relate to shoulder dystocia in America; (2) Skyrocketing malpractice premiums have forced capable doctors into early retirement; (3) Prodigious expenses of legal procedures have augmented the costs of maternity care; (4) The high costs of malpractice actions hindered the introduction of a national health care system; (5) Escalating brachial palsy cases required opening of neurosurgical units specializing in Erb's palsies; (6) Contradictory opinions have left doctors without guidance about the conduct of labor and delivery; (7) Obstetricians' obvious confusion has undercut patients' confidence in their knowledge and integrity; (8) The prevailing state of affairs turns capable medical students away from the specialty of obstetrics; and (9) Search for quick remedy obscures the fact that preventing birth injuries is the only long-term solution. Although contradictory views in medical publications dealing with this subject tend to confuse the picture, the basic issues are not particularly complex.

According to traditional thinking Erb's and Klumpke's palsies are physical injuries caused by use of excessive force during the extraction of the child from the birth canal. This concept is still favored by obstetricians in some foreign countries and probably everywhere by neurologists[15,21]. In contrast, among American obstetricians the idea that most injuries develop "*in utero*" spontaneously has gained wide acceptance[25-29]. It is understandable, that it struck a favorable cord in the hearts of practitioners. If Erb's palsies are spontaneous "*in utero*" injuries then there is no cause for self-doubt or self-reproach. Besides, this idea offers a firm ground for defending malpractice claims. If most injuries occur spontaneously, physicians are immune against litigations because it can never be alleged that "more likely than not" the damage derived from medical error. Formal acceptance of this concept would promptly end many obstetrical malpractice claims and could reduce insurance premiums by 40% or more. It is hardly surprising therefore that the arguments about the merits of the respective points of view have gone beyond the limits of disciplined academic dispute. Therefore, it amounted to an impressive example of professional integrity that a prominent protagonist of the "*in utero*" injury concept withdrew his initial claim when he recognized that the results of his animal experiments

Table 2 Birthweight distribution in 316 cases of fetal damage associated with shoulder dystocia[1]

Birth weights	Number of cases	Percentage of total
2500-2999 g	6	2%
3000-3499 g	20	6.0%
3500-3999 g	68	21.5%
=	=	=
4000-4499 g	107	34%
-	-	-
4500-4999 g	72	22%
5000-5499 g	32	10.5%
5500-5999 g	9	3%
⩾ 6000 g	2	0.5%

=: Traditional borderline for macrosomia; -: New American borderline for macrosomia. Based on traditional standards, less than 10% of all fetuses qualify for the definition of macrosomia. In this material 70% of all birth injuries were sustained by neonates belonging to this group. [1]Tables 2-4 show the results of mathematical calculations presented in previous publications. Copies of original articles containing details of the data analysis by the group's biostatistician can be obtained from the author.

Table 3 Birth weight associated risk of shoulder dystocia related fetal injury at delivery

Birth weight	National average	Sample	Estimated risk of damage
Under 3000 g	24%	2%	1:12000
3000-3249 g	17%	2%	1:8500
3250-3499 g	20%	4.5%	1:4444
3500-3749 g	16%	12%	1:3333
3750-3999 g	13%	9.5%	1:3368
4000-4249 g	5.5%	20%	1:275
4250-4499 g	3%	14%	1:214
4500-4749 g	0.8%	14%	1:57
4750-4999 g	0.3%	8%	1:37
5000-5249 g	0.2%	8%	1:25
⩾ 5250 g	0.2%	6%	1:33

In previous publications the author arbitrarily defined "acceptable" risk for fetal injury as 1% noting that the maternal risk of permanent injury in case of cesarean section is much lower. The table shows that the limit of acceptable risk is already exceeded at the 4500 g level and increases to 3%-4% when the fetal weight is 5000 g or more.

had been misinterpreted[27].

Conduction anesthesia during labor

Since it was recognized during the early days of spinal and epidural anesthesia that it had significant side effects, concern was expressed about the desirability of its routine use[30]. The untoward effects of conduction anesthesia fall into four major categories[31]: (1) Cardiovascular toxicity; (2) Maternal and fetal central nervous system toxicity; (3) Reduced uterine blood flow; and (4) Decreased uterine contractility.

Clinically, these effects manifest in convulsions, hypotensive episodes, cardiac arrhythmias leading to cardiac arrest and lasting neurological damage by injection into the spinal canal rather than into the epidural space. Eventually, in the absence of medical consensus it was women's demand that turned epidural anesthesia into a routine procedure[32].

Fetal macrosomia

Large fetal size plays a major role in arrest of the shoulders at birth[16,33-38]. However, it has been problematic to quantitate the magnitude of the risk[39]. Therefore, concern about increasing cesarean section rates induced professional organizations to encourage practitioners to deliver markedly large for gestational age (LGA) fetuses vaginally[40]. Apparently reassured by the claim that 50% or more of all brachial plexus injuries are spontaneous "*in utero*" events, as recently as 2002 and 2005 the ACOG[41] and the Royal College of Obstetricians and Gynaecologists (RCOG)[42] advised physicians to deliver fetuses of diabetic mothers weighing as much as 4500 g and those of non-diabetic women up to 5000 g vaginally and to use traction if the body does not soon follow the head.

In the course of a review of cases of shoulder dystocia related birth injuries that had occurred between 1960 and 2007 the author's group evaluated the distribution of birth weights of affected neonates[16]. The findings summarized in Table 2 show that a relatively small group of macrosomic babies suffered the overwhelming majority of injuries. The weight related increase of permanent damage showed a logarithmic curve rather than a geometric line. This finding implies that danger of underestimating fetal weight exceeds that deriving from overestimation.

Based on the above mentioned evidence the risks of damage for individual fetuses belonging to various weight groups were evaluated next. The calculation took into account the birth weight distribution in the United States[43] along with the information that about 1 out of 100 deliveries involve shoulder dystocia[44] and 1 out of 10 such newborn babies sustain permanent injury[45]. The results of this calculation are indicated in Table 3.

The investigated cases derived from 40 states or districts of the Union. The mothers' parity ranged from zero (112 cases) to more than six (4 cases). Maternal ages ranged from 13 to 45 years with the majority of them falling into the middle range. The ratio of male *vs* female neonates was 51:49.

Birth injures included 259 incidents of brachial plexus damage, 32 cerebral palsies, 6 cases of mental retardations, 16 developmental delays, 12 traumatic cerebral bleedings, one spinal cord dissection, and 8 perinatal deaths. The method of delivery was spontaneous on 200 occasions. Forceps were used for delivery 61-times, vacuum extraction on 41 occasions and both instruments (ventouse followed by forceps) 14-times. Several babies suffered multiple injuries. Three childbirths concluded by the Zavanelli maneuver[11] and cesarean section were included in the spontaneous vaginal delivery group.

According to reliable statistics[19], "in all series there is a two or threefold increase in the rate of cesarean delivery with high birthweight". This being the case, the gradually increasing frequency of fetal injuries in the LGA and macrosomic categories derived from a gradually diminishing number of vaginal deliveries of large fetuses. Obviously this circumstance biased the above presented results. When based on this knowledge the calculation

Table 4 Risks of shoulder dystocia related fetal damage in spontaneous and instrument assisted deliveries

Birth weights	Spontaneous deliveries	Instrumental extractions
Under 3500 g	1:5660	1:900
3500-3999 g	1:1740	1:110
4000-4499 g	1:204	1:24
4500-4999 g	1:41	1:6
⩾ 5000 g	1:25	1:3

Birth weight related fetal risks for damage in cases of spontaneous *vs* instrument assisted deliveries. Note that use of extraction instruments increases the chance for fetal damage almost 10-fold.

was adjusted, it transpired that the actual risks for lasting damage in these groups were more than 2.5% when the weight exceeded 4500 g and 5% when the child weighed more than 5000 g. Evaluation of these findings even on the ground of high school mathematics permitted the conclusion that widely quoted and relied on statistics[39,40] had grossly overestimated the number of cesarean sections needed for preventing of one fetal injury.

Arguments against elective abdominal delivery on the basis of estimated fetal weight have often included the warning that sonography was likely to overestimate the fetal size. Review of the literature clarified however, that in the 5000 g danger zone ultrasound examinations underestimated the fetal weight in 80% of the instances[46-48]. This fact indicates that the real danger associated with reliance on sonography is failure of identifying some excessively large fetuses rather than overestimating those who are not unduly large.

Because maternal risks associated with abdominal delivery are substantially less, in the writer's opinion a chance of 1% for permanent fetal damage is the acceptable maximum in contemporary practice. Even this liberal view incorporates obstetricians' traditional prejudice, namely that the mother's life is more precious than that of her unborn child. Consequently, the final arbiter of any relevant decision has to be the pregnant woman whose tolerance concerning maternal and fetal risks may differ from that of her obstetrician or of the consensus of medical opinion.

Instrumental deliveries

Observant obstetricians drew attention to the fact several years ago that mid-forceps extractions had markedly increased the incidence of shoulder dystocia[49]. By the same token, in the authors' material shoulder dystocia related fetal injuries had often been preceded by forceps or ventouse extractions. Between 1973 and 2006 not less than 117 records referred to instrumental deliveries[50]. When the material was distributed into weight groups (less than 3750 g/3750-4499 g/4500 g or more), it was learned that extraction instruments were frequently used in each of them (37%/40%/27%).

Comparison between the various technical procedures was hindered by two circumstances: (1) The ACOG elected to change the criteria of mid and low forceps operations in the 1980's. Since some physicians continued adhering to the old definitions, the documentations with regard to the actual types of the operations were often inconclusive; and (2) Whereas a statement pertaining to the nature of forceps operations usually appeared in the records, the majority of ventouse users provided no explanation.

Among those forceps procedures where the nature of the operation was stated 2 were performed at the outlet, 27 were low forceps and 29 mid-pelvic operations. Three forceps, one ventouse and one ventouse-forceps procedures were marked as "high".

Although in the entire material about two-thirds of the deliveries were spontaneous, the incidents of central nervous system (CNS) damage in the spontaneous and instrumental delivery groups were close to equal (37 *vs* 33). Thus, the use of instrument almost doubled the risk of CNS damage.

The data permitted a comparison between spontaneous deliveries on the one hand and extractions by instrument on the other. The result of this calculation is shown in Table 4. The tabulation indicates that in most categories the risk of major injury was more than 10-times higher when forceps or vacuum extractor was used than when unassisted delivery of the child was allowed.

This study does not support the claim that ventouse is more accident prone than forceps[51]. In fact the opposite was the case in this material. It transpires however, that both instruments augment the risks and that gradually increasing fetal weight increases them exponentially. The findings imply that one percent chance for fetal injury already prevails when extraction instrument is used for the delivery of a 4000 g fetus. Therefore, the author considers such a fetal weight the uppermost limit for a relatively safe extraction procedure in virtually any clinical situation. Undoubtedly, mid-cavity operations carry even higher danger.

Impaired glucose tolerance and diabetes

Routine glucose screening was not a requirement during those years while the medical records utilized for the here cited study were generated[52]. On this account evaluation of the predisposing effect for shoulder dystocia of maternal glucose intolerance was hindered. Only about two-thirds of all records contained reference to diabetic screening and some of these were not standard tests. Therefore, the information they provided was often equivocal. This circumstance limits the validity of the investigators' calculation, namely that whereas only 10% of all neonates weigh more than 4000 g in the general population, the rate is about 50% for diabetic mothers and 20% for those women with "predisposition" for diabetes[53]. Typically, positive screening test followed by negative 3 h glucose tolerance test was considered indicative of predisposition. In the > 4000 g weight group the risk of birth damage was 5-times increased for infants of diabetic mothers and twice for those of pre-diabetics as compared to others. Birth weights exceeding 4500 g seem to be 10-times more likely to occur among babies of dia-

betic women than among those of non-diabetic ones[16].

In light of the data reviewed routine diabetic screening of all pregnant women and attentive treatment of the disease are considered absolutely necessary. Although good management must take into account many relevant factors, including pelvic dimensions, previous births, maternal diet and others, in most instances an estimated fetal weight of 4000-4200 g represents for the author the uppermost limit for vaginal delivery in case of confirmed maternal diabetes. Assessment of fetal weight and size by ultrasound should be considered an obligatory routine in case of suspicion of LGA fetal status.

EFFECTS OF PRACTICE PATTERNS

During the 50 years covered by the studies of the author's group, routine management of labor has changed in many respects. It is necessary therefore to consider the potential effects of new developments upon the birthing process and its complications.

Oxytocin

When the drug entered the market it often caused uterine hyper-stimulation. Later it was only administered in intravenous drip under electronic fetal monitoring. Therefore this side effect became substantially reduced. This being the case, although it is suspected to increase the chance for shoulder dystocia, the drug is unlikely to be a major predisposing factor for arrest of the shoulders since it did not affect its rate during its relatively liberal use in clinical practice between the 1950's and 1970's.

Electronic fetal heart rate monitoring

Dysfunctional labor predisposes for shoulder dystocia. Designed to register uterine activity and evaluate fetal condition, external monitoring combined with tokography is useful and innocuous. By allowing the obstetrician to eliminate abnormal labor patterns and thus avoid difficult deliveries, electronic monitoring substantially reduced the number of factors conducive to brachial plexus injuries.

Fetal scalp blood pH determination

The technique is difficult, costly, labor intensive, in untrained hands inaccurate and carries the risk of causing fetal infection. It enjoyed popularity initially and was used with relative frequency for three decades. The technique largely disappeared from clinical practice by the early 2000's. It is unlikely that it influenced the rate of shoulder dystocia.

The "labor curve"

During the first half of the 20th century dysfunctional labor was tolerated for long periods of time because a cesarean section rate of 5% was considered the acceptable maximum. Friedman's[54] research pointing out the dangers of protracted labor changed physicians' thinking. Introduction of fetal heart rate monitoring that allowed recognition of "fetal distress" had similar effect. As a result, by the 1970's cesarean section rates rose to 10%-15%. The bush fire no longer could be stopped. At the turn of the century the rate of abdominal deliveries reached 30% and then increased even further. While it's other effects are disputable, this development was bound to reduce the incidence of shoulder dystocia and the related fetal injuries for more than one reason: (1) The fact alone, that the number of vaginal deliveries decreased by almost one-third allowed the expectation that shoulder dystocia would be reduced by the same rate; and (2) Many abdominal deliveries are done for protracted labor predominantly due to large fetal size[19]. Thus a high proportion of difficult vaginal deliveries that were conducive to shoulder dystocia became replaced by cesarean sections. In effect, changes that turned "obstetrics" into "perinatology" were such in nature that they were bound to cut the prevailing rates of shoulder dystocia and its related fetal injuries markedly. Obviously, any theory addressing the subject of causation must explain why Erb's palsies have continued to increase in America despite a marked reduction of its predisposing factors.

MISCELLANEOUS FACTORS AFFECTING INCIDENCE OF SHOULDER DYSTOCIA

The above mentioned change in the management of the birthing process that had escaped critical evaluation for several decades diverted the investigations of the author's group to new directions.

Geographic variations

The rates of shoulder dystocia differ in various geographic areas and at various time periods. Examples are its increasing rate in the United States[55,56], a high proportion of brachial plexus injuries deriving from a moderate number of shoulder dystocia incidents in Sweden[57,58] and its infrequent occurrence in the British Islands[42,59,60], Hong Kong[61] and Israel[62,63]. High birth weights of Swedish babies and relatively low weights of Chinese ones probably played a role in the quoted trends. This circumstance underlines the rule that conclusions based on one particular racial group do not always apply to others.

Chronologic fluctuations in the rates of shoulder dystocia

Disputes in America about the causes of shoulder dystocia have involved the contention that its incidence had not changed for decades[64]. The data presented in support of this claim included statistics from foreign countries where this complication had been rare. This arbitrarily mixed material did not reflect the state of affairs in the United States. Therefore, a computer search was undertaken. It yielded 20 reports that included 26 separate studies for the years of 1949-2005. The periods of observation ranged in the various studies from 1 to 10 years. The results deriving from these statistics are shown in Table 5.

Table 5 Incidence of shoulder dystocia in the United States between 1949 and 2005

Time periods (yr)	Number of reports	Ref. numbers of reports[1]	Average incidence per 100 births[2]
1949-1974	5	[55,65-68]	0.26%
1975-1990	10	[49,55,56,69,70-74]	1.22%
1991-2005	11	[56,74-81]	1.65%

[1]Two authors presented multiple reports; [2]Some reports referred to number of cases per 100 vaginal births. These were adjusted under the premise that the rate of cesarean section was 20%. Note that the rate of shoulder dystocia increased almost 5-fold by the 2nd and more than 6-fold by the 3rd time period as compared to the 1949 to 1974 average.

The data reveal that arrest of the shoulders occurred rarely (about 2-3 out of 1000 births) prior to the mid-1970's. Its rates rose rapidly thereafter until and including the first decade of the current century. In some services the increase was as high as 10 to 15-fold. Thus, rather than having remained stable cases of arrest of the shoulders and its neonatal consequences increased exponentially in the United States since the 1970's. This development appeared mysterious for a variety of reasons: (1) Changes in practice patterns eliminated or markedly reduced the number of predisposing factors for shoulder dystocia since the 1950's; (2) While the incidence of arrest of the shoulders increased in America its rate remained stable in the British Islands; (3) Circulars from medical organizations inundated practitioners with instructions about the prevention and management of arrest of the shoulders in recent years; and (4) Few issues of obstetrical journals appeared without studies discussing shoulder dystocia related problems.

Because the turnaround happened in the 1970's, the author elected to study those changes that had taken place in the practice of obstetrics around that time. This inquiry brought into focus two articles published by Wood *at al*[82,83] in the leading British specialty journal in 1973. Utilizing the at that time novel scalp blood pH technic during normal deliveries, these investigators found that after the emergence of the head the pH of the capillary blood fell at a rate of 0.04 to 0.14 units per minute although the neonates had excellent Apgar scores. Presumably because the technique was as yet unreliable at that time, these papers generated little interest in Great Britain. In contrast, they caused concern in the United States. Without explaining why, new editions of textbooks announced that the fetus must be extracted from the birth canal following the expulsion of the head without delay[84,85].

Wood *at al*[82,83] inconclusive research certainly deserved rechecking in order to assess its clinical relevance. However, things went the opposite way. Practice patterns were modified overnight but only quarter of a century later were scalp capillary pH levels studied during the head-to-body delivery interval in well-equipped laboratories by investigators who had experience with the technique. Aware of the clinical implications of their research their attention focused on babies who encountered shoulder dystocia. They found that delayed delivery of the body did not alter capillary pH significantly[80,86,87]. Investigations by Gurewitsch[88] based on more than 200 cases revealed that delayed delivery of the body caused no clinically significant change in the fetal metabolic equilibrium for up to 8 min.

Perhaps the most persuasive contribution to this subject was the investigation of Locatelli *et al*[23]. These research workers undertook a prospective study involving 789 patients who gave birth by the conservative method. It was found that the mean head-to-body interval was 88 s and the decline of the umbilical artery pH was only 0.0078 units per minute. They concluded that spontaneous birth did not significantly increase the risk on neonatal acidemia. Obviously, Wood *et al*[82,83] grossly overrated the decline of the fetal scalp blood pH during the delivery process. Thus, the reason for the still ongoing effort directed at shortening the head-to-body delivery time is difficult to understand.

In the opinion of the writer of this review the abrupt change in the management of the delivery process introduced into practice in the mid-1970's has been and remains the most important single factor responsible for the rapid increase of arrests of the shoulders at birth and the associated fetal neurological injuries in the United States.

It should be a matter of great concern that a group of investigators who had attempted in earnest to reduce the head-to-body interval to a minimum ended up with unprecedented 13.8% and 10.8% rates of arrest of the shoulders[89,90]. News of this "shoulder dystocia tsunami" raised no eyebrows among "fetal rescue" advocates. They reiterated a few years later: "Shoulder dystocia is an unpreventable obstetric emergency"[64].

Indeed, arrest of the shoulders is unpreventable if one prefers to believe that brachial plexus palsy has little to do with the method of delivery. Investigators who refrained from using traction during the birthing process, reduced the rate of this dangerous complication to the range of 0.2% without even trying[12,13].

On account of its adverse effect upon the practice of medicine, the fact that in the long run prevention of catastrophic birth injuries is the most effective approach to avoiding costly malpractice litigations deserves a brief mention in the context of the ongoing controversy[91].

Methods of delivery and shoulder dystocia

In order to evaluate the fetal effect of delayed delivery of the body after arrest of the shoulders, the writer's group reviewed in their medico-legal material those births that had occurred after 1974. Only 103 records documented the head-to-body intervals. Table 6 shows the relevant findings.

Table 6 Head-to-body delivery times in 103 cases of shoulder dystocia related neonatal neurological damage

Head-to-body interval	Number of cases
0-1 min	32
1-2 min	38
2-3 min	12
3-4 min	5
4-5 min	8
5-6 min	2
6-7 min	2
7-8 min	2
8-9 min	0
9-10 min	2

Note that in 82 instances (80%) delivery involving neurological injury of the child was accomplished within 3 min. Before 1973 these cases would not have been classified as shoulder dystocia. Because delay of the next contraction by 5 min does not endanger the fetus, the use of traction was unnecessary in the majority of these cases.

In a high proportion of the cases (42%) the 5 min Apgar score was less than five. Clinical experience shows that babies who are born spontaneously are in good condition even if the body is expelled with 5 min delay[11,88]. Thus, the low scores in this group most likely derived from stress caused by the extraction efforts.

Although the United Kingdom remained unaffected by the American shoulder dystocia crisis, the RCOG in 2005 endorsed the idea that the fetus must be extracted from the birth canal after the delivery of the head[42]. The "Guidelines" of the College cited the so called CESDI report in support of this advice stating that the investigation had found that 47% of babies who perished following deliveries complicated with shoulder dystocia "died within 5 min of the head having been delivered". Actually, members of the CESDI Committee emphasized that the adverse outcomes were unrelated to the head-to-body delivery intervals. They explained that the neonatal deaths had resulted from substandard management of the labor and inadequate skills on the part of doctors in charge[92]. The misleading misinterpretation of the official report by the RCOG Guidelines was duly pointed out by this writer's group in a recent review article sponsored by the Royal Society of Medicine in London[93].

Research performed one century ago utilizing fetal cadavers showed that typical brachial plexus lesions could be induced by applying strong traction upon the fetal head against resistance[94]. More recent experimentation conducted by French neurologists confirmed the earlier findings[95]. Utilizing sophisticated methodology Allen produced evidence that supported a relationship between aggressive management of the birthing process and neurological birth injuries[96]. He concluded based on his experiments that brachial plexus lesions sustained at birth were traction injuries and demonstrated that when encountering strong resistance, physicians subconsciously double the effort that the extraction of a child under normal circumstances requires.

Based on an extensive review Gurewitsch *et al*[97] concluded that "the single greatest correlate with neonatal brachial plexus injury after shoulder dystocia is (the) degree of clinician-applied traction".

Brachial plexus injury and cesarean section

Disregarding the fact that the observed cases of brachial plexus "paresis" had been only transitory, it has been proposed that babies born without any traction suffered brachial plexus damage (*i.e.*, "paralysis"). It has also been claimed that Erb's palsies are frequent among babies born by cesarean sections.

In the material that included 338 fetal injuries typically related to shoulder dystocia, only one child sustained Erb's palsy during abdominal birth. The case in question was a term delivery by elective repeat cesarean section. During the operation the surgeon found extensive adhesions at the area of the previous lower segment transverse incision. He could not create adequate opening and it was with great difficulty that the child was extracted eventually through a small incision. This incident was rare enough to deserve publication. Based on the stated details the article presented the opinion that most likely this child sustained typical traction injury[98].

Ubachs *et al*[99] analyzed 130 brachial plexus injuries of which 28 were associated with breech extractions. The authors noted that all vertex deliveries involved extensive manipulation and concluded that none of the cases could be attributed to "intrauterine maladaptation". They emphatically pointed out that no injury in their material had been associated with cesarean delivery.

Most obstetricians have encountered cases where delivery of the shoulders across a small incision cut through an uneffaced cervix caused as much difficulty as arrest of the shoulders during a vaginal birth does. This being the case it seems likely that most of those extremely rare brachial plexus palsies that are associated with abdominal deliveries are traction related.

PREVENTION OF SHOULDER DYSTOCIA AND BRACHIAL PLEXUS INJURIES: CONTROVERSIAL ISSUES

Because education pertaining to its management has little if any effect upon the rate of fetal injuries associated with arrest of the shoulders[100], this complication needs to be avoided as far as possible. Since prevention requires understanding of the cause of the problem[101], any prevailing theory has to be consistent with established facts in order to prove its validity. Therefore, advocates of the respective concepts must be able to answer several relevant questions: (1) Why did the rate of shoulder dystocia increase exponentially in the United States during the last 40 years in spite of the fact that changing practice patterns eliminated many of its predisposing factors? (2) Why did the rate of shoulder dystocia remain stable in Great Britain while it escalated in America? (3) Why do instrumental extractions increase the rate of brachial plexus palsies exponentially? (4) Why is brachial plexus injury literary rarity among neonates delivered by cesarean section? (5) Why is

maternal diabetes a strong predisposing factor for neurological birth injuries? (6) Why do most Erb's palsies occur in association with documented diagnosis of shoulder dystocia? (7) What experimental model supports the validity of the respective etiological theories? and (8) Does lack of diagnosis of shoulder dystocia indicate that Erb's was sustained spontaneously "*in utero*"?

The following are the answers of the author to these questions:

Question 1: The population of, and the living conditions in the United States have been stable during the 20th century. No new circumstance has emerged that could conceivably have caused fetuses to suffer Erb's or Klumpke's palsies *in utero* six-times more often than 50 years ago. The cause of the damage has to be therefore extrinsic.

Question 2: Up to 2005 the method of delivery remained conservative in the British Islands whereas it has been changed to "active" management in the United States. As a result, up to recently the rate of shoulder dystocia had been low in the United Kingdom[59,60,102].

Question 3: Should neurological injuries occur spontaneously *in utero* the use of ventouse or forceps could not affect their incidence. The documented relationship underlines the role of traction in the causation of injuries. Following instrumental extraction of the caput the uterus seldom expels the body within 30 or even 60 s. As a result, doctors adhering to active management are compelled to apply manual traction after the instrumental delivery of the head virtually invariably.

Question 4: Because 15% to 35% of all births involved the abdominal route in recent decades, the extreme rarity of Erb's palsy among cesarean babies is noteworthy. Obstructed labor accompanied by strenuous uterine activity is a frequent indication for abdominal deliveries. If the activity of the uterus had caused a significant proportion of brachial plexus injuries, Erb's palsies should be frequent among babies delivered by cesarean section on account of obstructed labor. However, this is not the case.

Question 5: Diabetes causes fetal macrosomia and broadens the shoulders out of proportion to the diameters of the head[33]. These effects predispose for arrest of the shoulders at birth and explain why big fetuses of diabetic mothers are particularly prone to suffering damage[50,53].

Question 6: The records reviewed by the authors were unselected and had been generated by many doctors and nurses in almost as many hospitals. Their references to shoulder dystocia were not influenced therefore by policies, interpretations or biases that may have been prevalent in some institutions or certain geographical areas. Had a high proportion of injuries been spontaneous "*in utero*" accidents there would have been no reason for them to coincide in > 90% of all instances with a complication (*i.e.*, shoulder dystocia) which only occurs once out of 100 deliveries.

Question 7: Experimental evidence supports the role of traction in the causation of Erb's and Klumpke's palsies[94,95]. No comparable evidence has been presented on behalf of the spontaneous "*in utero*" injury mechanism.

Question 8: This question is irrelevant to the pathological mechanism for several reasons: (1) The cause of brachial plexus injury is traction. Whether excessive pulling is done during or in the absence of arrest of the shoulders does not influence the mechanism of the injury; (2) With traditional delivery the criteria of shoulder dystocia are unequivocal. With active management the diagnosis is subject to the judgment of the accoucheur. It has therefore no objective validity; and (3) If one believes that the absence of shoulder dystocia proves that brachial plexus injury has occurred spontaneously "*in utero*", his or her judgment may become biased, even if subconsciously against acknowledging this diagnosis. Uninfluenced by such specious interpretation, more than 90% of the records in the author's data base that came from hundreds of different geographic locations, indicated that shoulder dystocia and brachial plexus palsies had occurred coincidentally.

Predicting shoulder dystocia

Reflecting unawareness of medical history, the dictum: "arrest of the shoulders cannot be predicted" has been repeated incessantly in recent years. Advocates of this truism must have overlooked that Jenner had not proposed only to vaccinate those unidentifiable children who had been singled out by Fate to contract smallpox. By the same token, Lind did not try to find out which ones of the embarking sailors for a voyage overseas would need a supply of fresh fruits in order to avoid scurvy. Similarly, Semmelweis did not restrict his aseptic measures to women whose destiny had been to roll in fever within a few days. Had these scientists wasted their time trying to "predict" the next victims of smallpox, scurvy or childbed fever, the secrets of these diseases would have remained unresolved for many more decades. In the same spirit, brachial plexus palsies must be avoided by general precautionary measures rather than by trying to determine who may need such protection next time.

Considering the present state of knowledge one must accept the probability that shoulder dystocia even in the best hands will continue to complicate two or three out of 1000 births for some time unless gifted soothsayers figure it out how to predict the victims. Until then, American obstetricians must live with the thought that only 80%-90% of currently prevailing brachial plexus palsies are preventable even if the urge of rescuing healthy babies from the womb is successfully resisted.

The causes of shoulder dystocia and the mechanisms of brachial plexus injuries are well understood. This problem is no different from many others that medical research has already resolved.

Basic principles concerning use of traction for delivery

It is a strange aspect of the shoulder dystocia controversy that the management of delivery is usually discussed as if long established concepts of modern obstetrics were fairy tales. Ever since the vacuum extractor had been

introduced into clinical practice it has been a rule that traction should only be applied at the time of uterine contraction[103]. This requirement ensures that expulsive uterine force supplements traction, thus eliminating the need for using undue effort. In violation of this concept, instructions governing the management of normal delivery encourage doctors to apply traction 30 or 60 s after the emergence of the head; the time when the contraction has just ended. As a result, the physician is forced to use more effort than would be needed if he waited for the next uterine systole. Although the latter would expel the fetus without intervention anyway, the risk of stretch injury could be already reduced if the obstetrician waited for a contraction and used traction in synchrony with it. That the condition of the fetus does not deteriorate between the contractions has been proven beyond any doubt[12,13,28,80,88]. Therefore, it defies elementary logic that an obstetrician who may have to wait several minutes for a contraction before delivering a severely compromised fetus with the ventouse, must extract a perfectly normal child by sheer force right after the expulsion of the head.

Medical errors leading to shoulder dystocia

Because the subject had been disregarded in the past, the role of the method of delivery in the causation of birth injuries has been stressed in this review. However, the records used for this research also revealed numerous departures from good obstetrical practice (not necessarily in conflict with minimum contemporary requirements) that were common denominators of the described accidents: (1) Assessment of the pelvic dimensions was often omitted or not documented in any detail; (2) Small maternal stature was ignored even if the mother was primigravida or had diabetes; (3) Frequently diabetic screening was either not done or equivocal test results were disregarded; (4) Confirmed diabetes seldom was treated effectively and only rarely with the involvement of an expert; (5) Excessive maternal weight gain seldom received attention and dietary instruction was rarely offered; (6) Frequently, not even by manual palpation was fetal weight assessed at or near term gestation; (7) Suspected LGA fetal status was not always evaluated with ultrasound; (8) Even if fetal macrosomia was suspected preparation for a difficult delivery was seldom made; (9) Some instrumental extractions of LGA fetuses were done without clear indication; and (10) Often only McRoberts maneuver, suprapubic pressure and manual traction were used for the management of shoulder dystocia.

It was a thought provoking feature of these unfortunate accidents that with relatively few exceptions not one single misjudgment but a combination of errors had led to neonatal injury. Correction of any one of them could have avoided the bad outcome on many occasions.

EPILOGUE

For physicians who due to indoctrination, habituation or temperament are addicted to rescuing babies from the birth canal the above shown list offers "Ten Commandments of Avoiding Shoulder Dystocia". With just a little luck they will find them helpful. For others who can be persuaded to allow mothers give birth naturally, the 11th Commandment: "Use two-step delivery!" may be the compass that guides them to the Promised Land where the rate of arrest of the shoulders is only 2-3 out of 1000 births. The return voyage there should not take another forty years. Some clever doctors from the United Kingdom, Israel, Ireland and Hong Kong have already found their ways there. Yet, it may be a worrisome journey for one who decides to sail across the Ocean of Misgivings with doubts in his mind, not unlike the sailors of Santa Maria did in the 15th century when they were still not quite convinced that the earth was round.

Having been accepted by too many obstetricians in the New World, belief in the ritual of reducing head-to-body delivery time and in the myth of "*in utero*" acquired Erb's palsies has become a matter of faith. "Faith can move mountains". Actually, it has already moved one when the ancient fortress of sound obstetric practice in London opened its gate and invited the trans-Atlantic Trojan horse inside its walls.

Lack of supporting evidence does not automatically sink attractive new ideas back into oblivion. More comforting is to think that the missing evidence is hidden somewhere nearby. The alternative would be to admit that well-meaning doctors have deceived themselves when they announced the discovery of a magic formula, capable of solving a distressing medical problem and putting the evil jinn of malpractice claims back into the bottle from where he had escaped. Alas, facts do not always prevail over wishful thinking. It is difficult for doctors who have done what they considered best for their patients to acknowledge that some of their activities were counterproductive. Ignatz Semmelweis was tormented by this thought throughout his life. Some others found easier ways out.

Almost two centuries ago Oliver Wendell Holmes presented a thesis which was important enough to be remembered thousand years from now. He eloquently, logically and correctly explained the cause and patterns of spread of puerperal fever[104]. His lecture included the unwelcome news that doctors who provided care for women in labor unwittingly transferred a deadly disease from one mother to the next. Having given due consideration to his already famous colleague's discovery, Professor Meigs one of the foremost authorities in obstetrics at that time, declared his own opinion. With one single sentence he may have sealed the fate of more women than the number of those whom all obstetricians in America saved from death during his professional lifetime. He also demonstrated that men incapable of seeing the difference between "belief" and "knowledge" could achieve distinguished reputation in medicine: "I prefer to believe"-he said-"that childbed fever is brought about by the will of Providence, which I understand, than that it is caused by an unknown contagion, which I don't"[105].

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MINIREVIEWS

Gynecological malignancies and hormonal therapies: Clinical management and recommendations

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Abstract

Every year in the world a large number of women receive a diagnosis of gynecological cancer and undergo a therapy such as surgery, chemotherapy and radiotherapy to the pelvic region. A large portion of these patients are already in menopause, but for younger patients therapies are responsible of early menopause. The physical and psychological symptoms due to iatrogenic menopause significantly reduce the quality of life; however hormone replacement therapy (HRT) has a high efficacy in reducing menopausal symptoms. The prescription of HRT in patients with story of gynecological cancer is debated because its safety has not been completely proven. The main criticism is based on the theory that the hormone replacement could stimulate growth of residual cancer cells increasing the risk of recurrence.

Key words: Iatrogenic menopause; Gynecological cancer; Hormone replacement therapy; Risk of recurrence; Climateric symptoms; Cardiovascular benefits; Clinical practice

Core tip: In this paper we analyze the role of hormone replacement therapy (HRT) in patients affected by gynecological neoplasms with iatrogenic menopause symptoms. We have analysed more than 70 articles with the aim to evaluate the possibility of using HRT in different gynaecological malignancies related to stage and grade of the neoplasm. The literature shows that the use of HRT is controversial in type I of endometrial cancer, endometrioid type of ovarian cancer, uterine cervix adenocarcinoma and endometrial stroma and leiomyosarcoma.

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INTRODUCTION

Hormone replacement therapy (HRT) consists in the administration of synthetic or natural female hormones to compensate the diminution or deprivation of natural hormones. Estrogenic therapy is useful in reducing menopausal symptoms like night sweats, insomnia, hot flushes, sexual disorder and dyspareunia[1-7]. Moreover Estrogens are effective in preventing the acceleration of bone turnover and the bone loss associated with menopause, and in reducing cardiovascular accident a diabetes insurence. HRT is the use of Estrogen alone (ERT) or, in women with an intact uterus Estrogen combined with a Progestin (EPT) to prevent endometrial proliferation

that can exacerbate an endometrial cancer. In fact, Estrogen brings an endometrial proliferation by increasing estrogen/progesterone receptors and cellular mitosis in the endometrial glandular epithelium. The association of Progestin creates a down-regulation of these receptors and moreover an induction of the activity of the 17 β-estradiol dehydrogenase which transforms Estradiol into Estrone that has an inferior activity. The association of Progestin thereby reduces the estrogenic stimulus on the endometrium[8]. Under the progestin influence, the histology of the endometrium changes from proliferative to secretive, and this reduces the risk of insurance of hyperplasia[9]. In the past 10 years much confusion has been generated regarding the use of HRT in the general population[10]. In fact HRT led to some important risk like breast cancer, venous thromboembolic events, stroke and coronary artery events[11]. After the publication of "Updated 2013 International Menopause Society recommendations on menopausal hormone therapy and preventive strategies for midlife health"[11] a general consensus on HRT has been agreed. However in oncological environment the use of HRT remains subject of debate. Women treated for gynecological cancer invariably incur the consequences of Estrogen deficiency due to the surgical resection of the ovaries, irradiation and chemotherapy[12]. Because of the underlying fear of cancer survivors, the insecurity of the clinicians, the lack of national or societal guidelines and the possibility of litigation should the woman develop a recurrence whilst taking oestrogen therapy, most clinicians do not prescribe HRT to these patients[12] regardless of tumour type and disease stage[13]. This has led to many women being denied the use of HRT thereby increasing the number of young patients who experience the effects of iatrogenic menopause. This is severely more intense than the natural onset both because of the sudden decline in estrogen/androgen levels and because of the younger age of the patients[14-16]. In particular severe hot flushes, vaginal dryness, sexual dysfunction, sleep disturbances, and cognitive changes may significantly affect quality of life[17]. The purpose of this review is to analyze the possibility of using ERT or EPT in patients who have been treated for gynecological malignancies with the aim of establishing recommendations for clinical practice.

RESEARCH

We reviewed the literature using the terms: HRT, ovarian cancer, cervical cancer, uterine sarcoma, endometrial cancer, borderline ovarian tumor. We analyzed more than 70 articles for the present study.

OVARIAN CANCER

Epithelial ovarian cancer

Epithelial ovarian cancer (EOC) is the most common type of ovarian cancer and the leading cause of gynaecological cancer related mortality[18,19]. It typically develops as an insidious disease[18,20,21], with few distinct symptoms until the tumour has become large or disseminated[19]. Currently, cytoreductive surgery combined with platinum-based chemotherapy is the standard treatment also for patients of child-bearing age. Cytoreductive surgery for a malignant ovarian tumour frequently results in the loss of ovarian function and menopausal symptoms[22]. HRT use for these patients is controversial because of the potential stimulation of residual cancer cells and the induction of new hormone-dependent disease[23]. Epidemiological investigations have suggested that malignancies of the genital tract may be associated with hormonal stimuli and with the ingestion of long-term oral estrogen[24,25]. *In vitro* experiments have yielded inconsistent results regarding the estrogen stimulation of cancer cell proliferation. Certain *in vitro* experiments have shown that estrogen is capable of stimulating the proliferation of malignant cells[26,27]. While some results of these studies showed tumour cell growth inhibition by estrogen[28], other authors found no effect of estrogen on malignant cell growth[29,30]. There are 4 different histological types of epitelian ovarian cancer: serous, endometrioid, clear cell and mucinous carcinoma. The 70% of EOC are serous type and probably derive from the ovary epithelium or the fallopian tube[23]. Endometrioid and clear cell tumours normally occur in patients that have ovarian inclusion cyst or foci of endometriosis. Endometrioid type of adenocarcinoma is similar to histological type of endometrioid adenocarcinoma of endometrium[31,32]. Endometrioid EOC express estrogen receptors and for this reason it is retained that HRT can stimulate post-surgical residual cancer. Even so, there are no studies that have shown a real association between HRT and the development of EOC after treatment[33]. Studies about HRT use after treatment of endometrioid cancer shows that HRT can be used in patients affected by early stage of endometrioid EOC. Although in patients with Stage 3 endometrioid adenocarcinomas because of the high possibility of residual disease after surgery the use of HRT is not secure in clinical practice[23]. Two meta-analyses with contrasting data about the impact of HRT on EOC follow up have been published, the first demonstrating no increase in relative risk of EOC in patients having HRT and the second demonstrating a little but significant raise in risk after long use (10 years plus)[34,35]. Different studies have investigated the possible adverse effects of HRT in patients who have undergone surgery and chemotherapy for EOC. Guidozzi *et al*[12] realized a prospective randomized study of 130 patients diagnosed with advanced stage, high grade serous ovarian cancer to analyze the effects of HRT on survival. That women who had earlier taken estrogens or had ovarian low malignant cancer were excluded. All of these patients underwent cytoreductive surgery and after cisplatin-based chemotherapy were randomized to have either oral Premarin *vs* placebo. After a follow up of 48 mo no considerable divergence in survival was noted between the two groups and the study establishing that HRT can be somministrated with the purpose of

Table 1 Epithelial ovarian cancer

Ref.	Study design	HRT *vs* control	Stage	Type of HRT	Months HRT	Months follow up	Recurrence HRT *vs* controls	Study conclusions
Eeles *et al*[37]	Retrospective case-control	78/295	1-2: 55% 3-4: 45%	Oral Estrogen Estrogen + Progestogen Estrogen + Tibolone	Median 28	Median 42	-	No effects of HRT on prognosis
Guidozzi *et al*[12]	Randomized controlled trial	59/66	1-2: 27% 3-4: 73%	Conjugate Estrogen	28	Mean 42	32 *vs* 41	No effect of HRT on DFS and OFS
Bebar *et al*[36]	Retrospective cohort study	31/0	NS	Non-conjugated-Estrogen + Progestogen	Mean 25	Mean 55	3	No effect of HRT on progression of EOC
Ursic-Vrscaj *et al*[38]	Retrospective case-control	24/48	1-2: 54% 3-4: 46%	Non-conjugated-Estrogen Estrogen + Progestogen Estrogen + Tibolone	Mean 24	Mean 49	5 *vs* 15	No effect of HRT on survival
Mascarenhas *et al*[33]	Prospective cohort study	649 EOC 150 BOT	1-2: 60% 3-4: 40%	Estrogen Estrogen + Progestogen	Up to 24	60	-	Better survival in HRT users *vs* non users
Li *et al*[39]	Prospective cohort study	31/45	1-2: 28% 3-4: 72%	Conjugated-Estrogen + Progestogen	Mean 28.7	Mean 31.4	-	No effect of HRT on cumulative survival HRT improve quality of life

HRT: Hormone replacement therapy; EOC: Epithelial ovarian cancer; NS: Not specified; BOT: Borderline ovarian tumor; DFS: Disease free survival; OFS: Overall free survival.

improving quality of life in young EOC survivors without increasing risk of recurrence[12].

A prospective cohort study by Mascarenhas *et al*[33] considered 649 women with EOC and 150 women with borderline ovarian tumours who were clustered according to pre and post cancer utilization of HRT using self-questionnaires. The work analyzed the effects of HRT before and after the diagnosis of both tumors on 5-year survival. There were found no significant divergence in EOC survival between the group of women who had HRT before cancer diagnosis and that who did not have it. Some data indicated a better survival for patients who had HRT before the arising of EOC, but there is not a clear explanation according to period or recent time of use. There are analogous data and no proof of an association between HRT use before diagnosis of endometrioid EOC was found. Better survival was reported for serous type women but a better survival after endometrioid tumours was suggested too[33]. A retrospective cohort by Bebar *et al*[36] describe 31 women with ovarian cancer treated with surgery and following chemotherapy who had non-conjugate estrogens for a mean period of 25 mo. Median follow up was 35 mo. Progression of disease occurred in only three patients, and one patient developed early stage breast cancer[36]. A retrospective study by Eeles *et al*[37] illustrated 373 women with endometrial cancer (EC) who had primary surgery after that, 78 of these patients had HRT in different formulations and 259 did not. In the group who had HRT there was a higher number of younger women most between the ages of 30 and 40 years, with earlier and well differentiated cancers. There was no considerable dissimilarity in disease free survival between those who had HRT and those who had not after checking for age, disease stage, tumor grade and interval to recurrence[37]. Ursic-Vrscaj *et al*[38] compared every patient with EOC at Stage I -Ⅲ treated with estrogen, with two non treated patients at the same stage of disease. They found similar disease free and overall survival in the two groups. Li *et al*[39] carried out a study aimed at assessing the impact of post-surgical HRT on life quality and prognosis in women with ovarian malignancies. HRT was administrated in 31 patients, 44 patients did not receive HRT. A long-rank test revealed no difference in survival between patients with and without HRT. HRT administered following surgery exhibited no apparent negative effects on prognosis in EOC, while post-surgical HRT aided in the stabilization of serum calcitonin levels and improved quality of life in these patients[39].

Current literature does not support the view that HRT facilitates the development and recurrence of ovarian cancer[36,38]. Thus, ovarian malignancy after clinical management of cytoreduction and adequate chemotherapy is not a contraindication for HRT. HRT may be a good option for patients with serious symptoms of menopause and osteoporosis. Nevertheless, the use of HRT still lacks the support of large-scale multi-center prospective double-blind randomized studies, particularly regarding its effect on tumour growth in patients with gross residual tumours. Therefore, care should be taken to limit the use of HRT as much as possible to patients with satisfactorily controlled ovarian malignancy. The suitable duration of HRT is currently under debate with no definite conclusions based on large-scale studies. Consideration should be given to an individual's specific clinical circumstances as well as the severity of menopausal symptoms. The results of the studies we have analyzed are listed in Table 1.

Borderline ovarian tumour

Borderline ovarian tumors (BOTs) comprise approximately 15%-20% of all epithelial ovarian malignancies[40,41]. They are known for their low malignant potential and for unclear associated risk factors. Patients with BOTs are, in general, younger than women with EOC: their average age at diagnosis is between 45 years old[42], and 30% of patients are less than 40 years old. BOTs can be unilateral or bilateral. Similarly to carcinoma, they can spread to the peritoneum and, eventually, to the lymphonodes[43]. Standard surgical treatment is based on bilateral salpingo-oophorectomy with or without hysterectomy. After comprehensive surgical staging, cystectomy or unilateral annessiectomy can be offered to patients who want to preserve their fertility[44]. However, young patients fot whom fertility-sparing surgery is not feasible (because of BOTs diffusion or recurrent disease) will suffer from iatrogenic menopause. For these patients HRT is an important issue. In 2006 Mascarenhas *et al*[33] showed that out of 150 patients with BOTs, 93% survived at least five years and out of these, 51% had used HRT after diagnosis. In 2012, Fischerova *et al*[45] concluded that HRT should be offered to these patients.

In literature, no prospective randomized study on HRT after BOTs was found, but we agree with the idea that HRT should be proposed in patients with bothersome symptoms for the same reasons that HRT is offered to patients with ovarian cancer.

Germ cell ovarian tumour

Ovarian germ cell tumors (OGCT) includes benign or maligna. Dysgerminoma, yolk sac tumour, embryonal carcinoma, polyembryoma, non-gestational choriocarcinoma, mixed germ cell tumours, and teratomas (immature, mature, and monodermal types)[46] are all OGCTs. The age of insurance is between 10 and 30 years of age[47]. Fertility sparing surgery is possible but most patients are submitted to adjuvant chemotherapy (*e.g.*, bleomycin + etoposide + cisplatin)[48] and radiotherapy. This results in a gonadal dysfunction leading to transient or permanent ovarian failure[49]. There is no evidence that hormones increase recurrence or decrease overall survival of ovarian cancer survivors and, although the research has been almost exclusively in epithelial ovarian cancer survivors, there seems to be no reason why HRT should not be given to survivors of OGCT[50]. On this basis, in 2009 Singh *et al*[23] concluded that these patients can benefit from the use of HRT.

Sex cord ovarian tumour

Sex cord-stromal tumours include granulosa cell tumours (GCTs), thecomas, Sertoli-Leydig cell tumours, gynandroblastoma. The most malign and the most common sex cord stromal neoplasms is GCT[51] which are also the most common. They secrete steroid hormones and diagnosis in frequently secondary to hypoestrogenism symptoms onset. Fertility preserving surgery can be offered in Stage 1 patients; a total abdominal hysterectomy with bilateral salpingo-oophorectomy is mandatory for all other patients[23]. Regarding the possible use of hormonal treatment to restore patients from menopausal symptoms, although no studies have been published, the general consensus is that HRT should not be used because of their hormone-dependent nature. In fact about 30% of GCTs are Estrogenic Receptor Positive and 100% are Progesteron Receptor positive[52]. In 2013, Guidozzi[50] confirmed that it may be prudent to avoid estrogen therapy in women who are survivors of ovarian stromal tumours, in particular if the tumour was a GCT.

EC

EC is the most frequent gynaecological cancer. We can divide EC into 2 different types: Type I is the endometrioid histotype, which express estrogen and progesterone receptor and normally has a low grade. Major risk factors are prolonged use of estrogen, obesity and physiological hyperestrogenism. Type Ⅱ EC normally has a serous-papillary or clear cell histotype, it doesn't express Estrogen and Progesterone receptors and habitually it has a high histological grade and for this reason it is more offensive than type I [53]. This malignancy principally affects post-menopausal women, although about 20%-25% of women with EC are pre-menopal and about 5% have less than 40 years of age[54]. This cancer is normally diagnosed at an early stage (85% of patients in Stage I or Ⅱ) because of abnormal uterine bleeding as a prevalent symptom of the neoplasm[55]. Surgery represents the principal treatment: the typical surgical intervention is total hysterectomy and bilateral salpingo-oophorectomy to leave out the risk of ovarian metastasis or ovarian cancer. In advanced stages or precarious clinical conditions of the patient the primary treatment is radiotherapy. Because of the important role played by estrogens in the onset of the most common endometrial cancer, HRT may stimulate the growth of occulti tumour cells remaining after surgical treatment. For this reason replacement of this hormones after disease treatment seems to be contraindicated. However there is no evidence that HRT may adversely affect disease free survival and the recurrence rate in women treated for endometrial cancer[56,57]. Several studies have analyzed patients affected by endometrial cancer treated with HRT to reduce iatrogenic menopausal symptoms. Creasman *et al*[58] and Lee *et al*[59] in 1986 and in 1990 respectively, published case control studies on HRT in endometrial cancer Stage 1 patients finding a lower recurrence rate, longer disease-free and overall survival in users against non-users. In fact in the Lee series no recurrences occurred in estrogen users while HRT had been prescribed only in patients with low risk of recurrence (Stage 1A or 1B and low grade). The control group had a higher recurrence rate because of the higher-risk disease (Stage 1C grade 3). When only low-risk patients were compared Lee found no difference in recurrence rate. In 1990 two separate retrospective studies published by Bryant[60] and Baker[61], examined

Table 2 Endometrial cancer

Ref.	Study design	HRT *vs* control	Stage	Type of HRT	Months HRT	Months follow up	Recurrence HRT *vs* controls	Study conclusions
Creasman *et al*[58]	Retrospective case-control	47/174	1	Oral/Vaginal/Oral + Vaginal Estrogen	Mean 32	25-150	2 *vs* 15	Estrogen has a good effect on DFS an OS
Lee *et al*[59]	Case-control	44/99	1	Oral Estrogen	Median 64	24-84	0 *vs* 8	Estrogen are safe in low risk patients
Bryant[60]	Retrospective cohort	20	1-2	Conjugated Estrogen ± Depo Provera	12-132	42-168	NS	No recurrences in patients treated with HRT
Baker[61]	Retrospective cohort	31	NS	Oral/Vaginal/transdermal Estrogen		192	NS	No increase of recurrence or mortality in HRT users
Chapman *et al*[62]	Retrospective case-control	62/61	1-2	Oral/Vaginal Estrogen ± MPA 2.5 mg	Mean 49.1	Median 57.1	2 *vs* 8	No decreased DFI or increased recurrence in users *vs* non users in early stage
Suriano *et al*[63]	Retrospective cohort with matched controls	75/75	1-3	Oral Estrogen ± MPA 2.5 mg	Mean 83	Mean 83	2 *vs* 11	HRT ± Progestogen do not increate recurrence rate
Barakat *et al*[64]	Randomised double blind trial	618 *vs* 618	1-2	Oral Estrogen	Planned 36	Median 35.7	14 *vs* 12	Not completed. Low recurrence rate
Ayhan *et al*[65]	Prospective case-control	50/52	1-2	Conjugated Estrogen + Progesteron	Mean 49.1	Mean 49.1	0 *vs* 1	Postoperative HRT did not increase recurrence or death rate

HRT: Hormone replacement therapy; MPA: Medroxyprogesterone acetate; DFS: Disease free survival; OS: Overall survival; DFI: Disease free interval; NS: Not specified.

cancer survivors who received estrogen therapy after treatment and were followed up for 4-16 years. The stage of neoplasm was I - II in the Bryant study and was not specified in the Baker study. No recurrence of endometrial cancer was noted in either the studies. Chapman *et al*[62] examined women with stage 1 or 2 EC. There was no significant difference in recurrence rate between HRT users and non-users, however the groups were not homogeneous because patients in the non-users group had often a greater frequency of high grade and stage, and were older than patients submitted to HRT. In the year 2001 Suriano *et al*[63] studied women affected by stage I - II - III of EC and described a longer disease-free interval in HRT users *vs* non-users with a significant difference ($P = 0.006$). The study concludes that HRT with or without progestins does not seem to increase the risk of recurrence or death in patients treated for EC. The only randomized study was carried out by Barakat *et al*[64] in 2006. It started in 1997 and stopped in 2003 after the publication of the Women's Health Initiative results that made accrual impossible. For this reason they did not reach their goal of 2108 patients but they randomized 1236 patients who received either estrogen or non-estrogen therapy after undergoing surgery. The authors concluded that, although the study could not clearly define the safety of estrogen therapy in endometrial cancer survivors, there is a low recurrence rate (2.1%) and minimal incidence of new neoplasm. Ayhan *et al*[65] published in 2006 the first prospective case control study which showed that HRT administered immediately after surgical intervention did not amplify the recurrence or the mortality rate in Stage 1 and 2 EC survivors. The main limitation of this study was the small sample size and lack of randomization. These results were shown in a 2010 review by Singh *et al*[23]; however the author underlined that in endometrioid cancer of the endometrium the reason why HRT did not showed adverse effects may be due to the radical tumor excision because of early stage. In fact in advanced stage Type I of endometrial cancer there may be some residual cells after surgical treatment that can be stimulated by HRT and subsequently change the prognosis of the patient. The use of estrogen-progestogen HRT would probably suppress estrogen stimulated cell growth because of the progestogen combination, but there are no clear evidence data about this theory[23]. The studies listed above are resumed in Table 2.

UTERINE SARCOMA

Uterine sarcomas constitute a disparate category of malignancies which includes leiomyosarcoma (LMS), endometrial stromal sarcoma (ESS), undifferentiated endometrial sarcoma and carcinosarcoma. The data available in literature on the role of estrogen therapy after surgical treatment for uterine sarcomas are limited because they are uncommon tumors (3%-8% of all uterine malignancies in women). Most ESSs express steroidal receptors and are considered to be hormone-sensitive. Many studies have shown a regression or stabilization of recurrent low-grade ESS with endocrine therapy based on medroxyprogesterone acetate and Letrozolo (aromatase inhibitor)[66]. Patients with a history of ESS should not be treated with estrogen therapy or tamoxifen and, if present, withdrawal of estrogen therapy is strongly recommended[67]. LMSs are the most common

Table 3 Recommendations

Site	Tumour type	HRT
Ovary	EOC	
	Endometrioid	No[1]
	Others	Yes
	Germ cell ovarian tumour	Yes
	Sex cord ovarian tumour	No
Uterus	Endometrial cancer	
	Type 1	No[1]
	Type 2	No[1]
	Uterine sarcoma	
	Endometrial stroma sarcoma	No
	Leiomyosarcoma	No
Cervix	Adenocarcinoma	No
	Squamous	Yes

[1]To evaluate in a multidisciplinary team. HRT: Hormone replacement therapy; EOC: Epithelial ovarian cancer.

of uterine pure sarcomas (42%-60%) and some express estrogen and progesterone receptors at different levels. Avoidance of estrogen therapy is generally recommended in surgically treated women with LMS because of their potential hormone sensitiveness[68].

CERVICAL CANCER

Cervical cancer is the second most common gynaecological cancer with an important mortality and morbidity. Due to pap-test screening early diagnosis and therapies are increasing leading to a larger population of young women facing collateral gynaecological symptoms. Although fertility sparing treatment is possible in early stages, in advanced stages treatment consists of either radical surgery or primary chemo-radiotherapy. In squamous carcinoma, almost 80% of cervical cancers, ovary preservation is usually feasible and safe due to the low metastasis rate however for adenocarcinomas oophorectomy is usually recommended. Women with cervical cancer often undergo external radiotherapy or brachytherapy causing significant toxicity to the vagina. In addition to symptoms caused by iatrogenic menopausal status this may result in vaginal stenosis, dyspareunia and major sexual problems. Generally HRT is not refused in patients who complain of menopausal symptoms after treatment for squamous cervical cancer (SCC)[69]. SCC is not considered an estrogen responsive tumour even though estrogen receptors have been described in this tissue too. A study by Ploch[70] on 120 women showed no change in the survival rate or Disease Free Survival at five years in patients receiving HRT after treatment for cervical cancer Stage Ⅰ/Ⅱ. A higher risk seems to exist for cervical adenocarcinoma. It has been suggested that it should be treated in the same way as endometrial cancer because of the dependence of this histotype on oestrogen stimulation[71]. The adverse effect of radiotherapy like vaginal stenosis can be treated with local oestrogen subministration but there is no clear evidence about a linkage between hormonal therapy and a worse prognosis of cervical cancer[23].

BRCA MUTATION CARRIERS AFTER SALPINGO-OOPHORECTOMY

Women with germ line BReast CAncer type 1 (*BRCA1*) or *BRCA2* mutations have higher life time risk of ovarian (15%-56%) and breast (45%-80%) cancers than the general population (ovarian cancer 1.4%; breast cancer 12%)[72]. In women between 35 and 40 years old profilactic annessiectomy is recommended to reduce the risk of insurance of ovarian malignancies, causing the insurance of iathrogenic menopause with deterioration of quality of life. Two observational studies in women with *BRCA* mutation treated with prophylactic salpingo-oophorectomy showed no increase of breast cancer incidence in HRT users[73,74]. On the contrary, Million Women Study compared HRT users with non users receiving placebo and it demonstrate an increased risk of breast cancer in the first group of patients[75]. Current studies of women carring *BRCA2* mutation are non randomized and there is little data about the increased risk of breast cancer in this group of patients.

Because of the increased risk of osteoporosis, cardiovascular event, cognitive problems and vasomotor symptoms related to hyatrogenic menopause, we agree with the idea that short-term HRT should be propose[76].

CONCLUSION

HRT with Estrogen or Estrogen and Progestogen is the therapy with the highest efficacy in the treatment of physical and psychological symptoms of iatrogenic menopause. HRT can be administered in women with story of squamous cells carcinoma of the uterine cervix; conversely should not be prescripted in patients with endometrioid ovarian carcinoma, atypical histologies endometrial carcinoma, borderline ovarian tumour, germ cell ovarian tumours and *BRCA1-2* mutation carrier patients. The use of HRT in endometrioid EOC and endometrial cancer is debated because there are no studies that come to an agreement on this topic. We can speculate that the use could be stage-dependent, but in any case HRT should be discussed in a multidisciplinary team. HRT use is not safe endometrioid endometrial cancer, endometrioid ovarian cancer adenocarcinoma of the uterine cervix, endometrial stroma sarcoma and leiomyosarcoma. In these groups of patients non hormonal therapies are rational alternative to HRT to reduce vasomotor symptoms. These recommendations are resumed in Table 3. HRT should start after six months from the last treatment (chemotherapy or radiation therapy) to reduce thrombotic risk due to cancer, chemotherapy and hormone therapy.

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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

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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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