**SLE Nephritis and Pregnancy: Concerns and Management**

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**Abstract**

Pregnancy associated with lupus, especially lupus nephritis, is often fraught with concern for both mother and fetus. Thus, it is paramount that care begins pre-conception so that proper planning in terms of optimizing the medical regimen, discontinuation of fetotoxic agents and treatment of active disease can occur. It is well known that active nephritis at the time of conception is associated with poor outcomes. Even with quiescent disease, recent data indicate that being lupus anticoagulant positive, non-white or Hispanic and using antihypertensive medications were all predictors of worse pregnancy outcomes. Further, prior lupus nephritis also predicts higher rates of preeclampsia and HELLP syndrome. Differentiating lupus nephritis from preeclampsia often presents as a conundrum, but the former can be confirmed by the presence of decreasing complement levels and rising anti-double-stranded DNA in addition to new onset hypertension and proteinuria. We hope that the more mechanistic approach of measuring angiogenic markers, which are diagnostic for preeclampsia, will be the standard of care in the future. Women with lupus and prior lupus nephritis can have successful pregnancies, but much is dependent on "the art of planning" as well as close communication between the obstetrician, the nephrologist and the rheumatologist.

**Keywords:** Lupus nephritis, pregnancy, preeclampsia

## Introduction

Women with lupus, especially lupus nephritis, may be at increased risk of obstetric and fetal problems in pregnancy as well as problems related to their disease. The key to successful outcomes is joint planning before pregnancy with a nephrologist well versed in high-risk pregnancies in order to assess and minimize the risks. The woman needs to know about optimal timing, medication management and be aware of the potential pitfalls (Table 1). Of course, many women with lupus present for the first time during pregnancy, and the key to optimizing their outcomes is making the diagnosis quickly, initiating appropriate treatment along with immaculate fetal and maternal multidisciplinary care in an appropriate tertiary setting where available.

## Pre-Pregnancy Planning

Women with lupus face increased risks to themselves and to their fetus during pregnancy and should be offered pre-pregnancy planning. Since several of the drugs used to treat lupus and/or lupus nephritis are teratogenic, it is critical to explore a woman's wish to become pregnant very early on in management.

### *Fertility*

The first issue to consider is her fertility. Lupus does not impair fertility, but use of cyclophosphamide may do so, [1] as may advanced kidney impairment. Note how long the woman may have been trying to conceive, how much cyclophosphamide she has had and the degree of renal dysfunction. Regular periods do not confirm fertility, but clearly amenorrhoea should put the physician on guard. Importantly, many women with lupus will have been advised to avoid pregnancy whilst their disease is active and may have been using long acting forms of contraception and have no notion whether they have regular periods or not.

Depending on the woman's age, but also bearing in mind this is a relapsing remitting disease, it is worth referral to an infertility expert sooner rather than later in women with lupus who have difficulty conceiving.

***Timing***

The next element to focus on is timing. A women should be advised her lupus needs to be inactive for at least 6 months before attempting to conceive. This is particularly true if she has active lupus nephritis. In reality, the advice should be given on first meeting a patient with a flare of their disease that requires an increase in treatment. My stock phrase at that point is "You will have your baby, but not yet". For women with lupus nephritis, it is safest to talk in terms of at least a year, bearing in mind the average time to remission is around 9 months, and they then may need to change their maintenance therapy to a baby friendly drug and prove they can tolerate the new medication and remain stable. Of course the advice will be tempered according to the age of the woman, her degree of kidney impairment and the severity of her disease, but the rule of thumb is that her disease should be quiescent for 6 months prior to conception.[2,3] There are good data to show that commencing a pregnancy with active disease is associated with remarkably worse maternal and fetal outcomes. [2]

***Pharmacological Management***

This is a crucial part of planning for pregnancy in a woman with lupus. It is just as important to advise on medications they should not stop and the medications they should start in advance or soon after conception, as to advise on medications they must avoid when trying to conceive. The aim is to maintain them in remission so, unless planning well in advance, this is not the time to wean them off maintenance medications such as low dose prednisolone and azathioprine. If they are on low dose aspirin they should remain on it and if not, should plan

to start it once pregnant to reduce the risk of preeclampsia. Hydroxychloroquine reduces the incidence of flares, infections, thrombosis and is associated with better long term renal survival.[4,5] Importantly, it appears to reduce the risk by 50% of congenital heart block in babies of mothers who are anti Ro positive, [6] including data from the recent PROMISSE study.[7] It crosses the placenta, but extensive experience has shown no increased risk of miscarriage, congenital defects or fetal death.[8] Importantly, exposed children have been shown to have no visual or hearing impairment and have normal development. [4,9,10] A recent paper suggests that it may also reduce the risk of intrauterine growth restriction.[11] If a woman is taking a calcineurin inhibitor (cyclosporine A or tacrolimus), these are also safe to continue in pregnancy. Any woman trying to conceive is advised to take folic acid.

Many women with previous lupus nephritis have a degree of persistent proteinuria and hypertension – both these are bad prognostic features in themselves for fetal outcomes.[3] Importantly, many women when not pregnant will be on renin angiotensin system blockade (RAS). These are contraindicated beyond the first trimester because of high rates of fetopathy. Advice to women with lupus nephritis and residual or minimal proteinuria is to stop the RAS blockade pre-pregnancy to evaluate the level of proteinuria while off this regimen and to establish pregnancy-safe anti-hypertensive treatment so that blood pressure can be adequately controlled. If the proteinuria off the RAS blockade rises to more than the equivalent of 1g/day, the woman is advised to have a renal biopsy to exclude active nephritis. If there is active lupus nephritis, clearly pregnancy should once again be delayed until complete remission can be achieved with immunosuppression. Should proteinuria be the result of renal scarring alone, stopping RAS blockade upon conception is reasonable. The management of hypertension in pregnancy is discussed in "New Evidence in the Management of Chronic Hypertension in Pregnancy" in this special issue.

Medicines commonly used in women with lupus, especially those with lupus nephritis, that must be stopped pre-pregnancy are mycophenolate mofetil (MMF), cyclophosphamide (CyP), rituximab and methotrexate. MMF is teratogenic, associated with increased fetal loss and should be avoided during pregnancy.[12] A constellation of structural abnormalities is now recognized, and these include microtia, external auditory canal atresia, orofacial clefts, cardiovascular malformations and digital hypoplasia.[12,13] Recent registry data comparing 302 women who discontinued MMF before conception with 142 who took MPA in the trimester, show a higher rate of miscarriage in those with first trimester exposure (48% vs. 20%, $p<0.001$) and birth defects (11.6% vs. 5%, $p=0.01$). [14] As such, women on MMF in early pregnancy are less likely to have a live birth. [13,15,16] In practice, we advise all women on MMF not to get pregnant and that they will need to stop and switch to azathioprine prior to conception – the current advice is to switch 90 days before conception, allowing time for assessment of tolerability and safety on pregnancy safe immunosuppression. Studies have shown it is safe to switch to azathioprine as maintenance immunosuppression, though flares do occur – often pre-pregnancy, which sets the woman back months or years in her plans for conception. There is no simple solution to this dilemma and women simply need to be warned.

Prior to starting azathioprine a thiopurine methyltransferase (TPMT) test is recommended to evaluate the safe starting dose of azathioprine. The activity of the enzyme TPMT is regulated by a common genetic polymorphism, 1 in 300 individuals lack enzyme activity and 11% are heterozygous for a variant low activity allele. Myelosuppression is much more common in those who lack or have low activity and prior knowledge influences initial dosing. The maximum dose to use in pregnancy is 2mg/kg/day.

***Pregnancy Outcomes***

When advising women what is likely to happen to them in pregnancy, the data to draw on now include a systematic review, two large multicentre prospective studies as well as many smaller retrospective analyses (Table 2). There are also new guidelines published this year from EULAR. [17] Risks to mom include a flare of their underlying disease, which can result in loss of renal function as well as both the short and long-term health risks associated with severe preeclampsia. The risks to the baby of mothers with lupus include higher rates of miscarriage if lupus anticoagulant positive, prematurity (spontaneous and iatrogenic) especially if the mother develops preeclampsia, being small for gestational age and if very premature, clearly the baby is at risk of death or permanent disability.

Smyth et al in their systematic review of 37 studies spanning 1980-2009 (so multiple treatment modalities and varying levels of obstetric and neonatal provision) of 1842 patients and 2751 pregnancies showed that a lupus flare of any sort was common (25.6%), hypertension was seen in 16.3% of women, lupus nephritis in 16.1%, preeclampsia in 7.6% and eclampsia/stroke or death in approximately 1%.[18] These are all major issues for women as they will lead to the need for increased medication, possibly worsening renal function and likely early delivery. Of note, active nephritis at the time of conception or a history of prior nephritis were perhaps, unsurprisingly, both significantly associated with maternal hypertension ($p<0.001$), but only prior lupus nephritis was associated with an increased risk of preeclampsia ($p=0.017$). The presence of antiphospholipid antibodies was also associated with hypertension ($p=0.029$). The review described unsuccessful pregnancies in a large proportion of women (23.4%) though this was over a 30 year period from 1980-2009.[18] Prematurity defined as delivery at <37/40 was also frequent (34.9%). Stillbirths occurred in

3.6% of pregnancies, neonatal deaths in 2.5% and intrauterine growth restriction (IUGR) in 12.7%.

The recently published PROMISSE study from Jill Buyon's group is a large prospective study from the USA and Canada of 385 women from multiple ethnic and racial backgrounds.[7] It is informative as it excluded women with active nephritis or active systemic disease as defined by a urine PCR > 1000 mg/g, creatinine level greater than 1.2 mg/dL, daily prednisolone use >20mg/day and twins – i.e. these were all women with largely quiescent disease at conception. The women were followed from the first trimester, all were looked after in specialist centres and nearly all were on hydroxychloroquine. The endpoints of adverse pregnancy outcomes were hard measures:

1) Premature birth (<36weeks) due to gestational high BP, preeclampsia or placental insufficiency
2) Small for gestational age (birth weight <5$^{th}$ Centile)
3) Fetal death during 2$^{nd}$ or 3$^{rd}$ trimester
4) Infant death related to pregnancy problems

The study results highlight some very important messages for women with lupus or quiescent lupus nephritis. Overall, 81% of 236 women had uncomplicated pregnancies and fetal and infant deaths were very rare. Severe maternal flares in the second and third trimesters occurred only in 2.5% and 3.0%, respectively. Importantly, the study identified what constituted risk for adverse pregnancy outcomes. The 129 women who were non Hispanic white, not receiving anti-hypertensive agents, lupus anticoagulant (LAC) negative, had a physician's global assessment score of 1 (i.e. mild or no disease activity) or lower at screening, and a platelet count of at least 100 x $10^9$ cells/l, only 10 (7.8%), had low rates for any adverse pregnancy outcomes (7.8%) and the fetal or neonatal death rate was only 3.9%.[7] In contrast, in the 50

women who were either LAC-positive or LAC-negative, but non-white or Hispanic and treated with antihypertensive agents, the adverse pregnancy outcome rate was very high at 58% with a high proportion of events occurring between 23 and 35 weeks gestation, and the fetal or neonatal death rate was 22%. Clearly this will be relevant to many women with prior lupus nephritis many of whom will be on antihypertensive agents, but what needs to be stressed to patients, however, is that the majority of these women had quiescent disease, were in specialist centres and were nearly all on hydroxychloroquine.

A multicentre study from Italy, published just this year, prospectively followed a group of 61 women with lupus nephritis through 71 pregnancies over the years 2006-2013.[11] All the women had pre-pregnancy counselling so their management was optimized. At the time of conception, the majority (78.9%) were in complete remission and the rest had mild active LN as defined by proteinuria >500mg/day – a fairly generous definition of activity. Flares, as defined by pretty modest increases in proteinuria that may or may not have been true flares, occurred in 14 women (19.7%) and all responded to treatment. Flares were predicted by low C3 and high dsDNA at baseline. Preeclampsia was seen in 8.6% - a figure remarkably similar to that found in Smyth's systematic review and two women developed HELLP. Preeclampsia and HELLP were predicted by prior lupus nephritis, longer disease duration and hypertension. The fetal loss rate was 8.4% and was predicted by hypertension at baseline, being LAC or anticardiolipin antibody positive and triple positive for anti-phospholipid antibodies. Preterm delivery occurred in 28.2% and was predicted by high baseline SLEDAI (lupus activity score), proteinuria, history of renal flares, hypertension and active lupus nephritis. The odds of a preterm delivery increased by 60% for each quarterly unit increase in lupus activity (SLEDAI) and by 15% for each increase in proteinuria by 1 g per day. IUGR was seen in 16.4% of babies, and importantly the probability was reduced by 85% in women who were taking

hydroxychloroquine. This study again highlights the importance of pre-pregnancy optimization for better pregnancy outcomes.

What these prospective studies now offer is contemporary era data with which to advise women of the risk. Overall, the message is optimistic – most women with inactive lupus will have uncomplicated pregnancies. Considering many women in the past were advised against having a baby simply on the basis of having had bad lupus, we can now be more confident in advising them of risk, providing good advice on timing and ensuring they are well prepared for pregnancy. However, the pregnancies are not risk free for either the mother or baby, and most women with prior lupus nephritis should be treated as high risk and need care from a high risk multidisciplinary team that includes expert obstetric and renal/rheumatological care. An important message for women is that even if they have had a prior pregnancy that ended badly there are good data to suggest that the second pregnancy is often absolutely fine, not least because they go in with planning, in remission and under high-risk care.

**Fetal and Pregnancy Surveillance**

The recent EULAR guidelines suggest enhanced fetal surveillance by ultrasound in women with lupus/antiphospholipid syndrome.[17] Over and above routine first and second trimester screening, there should be supplementary fetal surveillance in the third trimester at monthly intervals, which should include Doppler sonography of the umbilical artery, uterine arteries, ductus venosus and middle cerebral artery (particularly in fetuses that have been identified to suffer from early IUGR, i.e., prior to 34 weeks of gestation). Additionally, in cases of late IUGR (diagnosed after 34 weeks), reduced abdominal circumference growth velocity and/or a reduced cerebroplacental ratio at Doppler investigation can identify fetuses at higher risk of poor perinatal outcome (Doppler of the umbilical artery alone is insufficient).

Additional fetal surveillance is needed for those women who have anti Ro antibodies, which are linked to the development of neonatal lupus, including a low risk (0.7-2%) for congenital heart block (particularly if the antibody titres are high). The EULAR guidelines recommend fetal echocardiography in cases of suspected fetal dysrhythmia or myocarditis, especially in patients with positive anti-Ro/SSA and/or anti-La/SSB antibodies.[17] Many centers routinely screen all Ro+ve women with fetal echo at 16-18 weeks gestation.

***Differentiating a Flare of Lupus Nephritis from Preeclampsia***

Once pregnant, two issues over and above those already described challenge mothers and physicians: 1) Does the presence of increasing proteinuria and hypertension represent a flare? 2) Does the presence of increasing proteinuria and hypertension represent the onset of preeclampsia? Whilst early in pregnancy the presence of new or worsening proteinuria and hypertension will almost always represent a flare of lupus nephritis, beyond 24-26/40 weeks of gestation differentiating a flare from preeclampsia poses a challenge both diagnostically and therapeutically.

Flares of lupus nephritis in pregnancy may be the first presentation of lupus, and are relatively rare in those without prior nephritis or inactive nephritis at the start of pregnancy. However, if a woman presents with increasing proteinuria, hypertension ± impaired function early in pregnancy and has lupus, then it is very likely she is having a flare of lupus nephritis. As always history is key, supplemented by appropriate investigations. Pregnancy is essentially a state of the acute phase response so complement should be normal or high. Falling complement, even within the normal range, should raise the alert that lupus is becoming more active. The same is true for rising dsDNA antibody levels. If the proteinuria

is significant and unexpected and likely to lead to a change in immunosuppression then in the first trimester and part of the way through the second trimester, renal biopsy can be considered. The risk is not increased by pregnancy, but what has to be weighed is should the woman have a post biopsy bleed, how long can anticoagulation safely be delayed in a pregnant woman with heavy proteinuria, possible antiphospholipid antibodies, and therefore, at very high risk of venous thromboembolism. If the risk of the latter outweighs the benefit of a firm diagnosis, do not biopsy. If the patient has serology in keeping with a lupus flare, has had nephritis before and appears to have nephritis again, then a biopsy is also less warranted.

Distinguishing lupus nephritis from PET later in pregnancy (from 26/40 weeks of gestation) can be much more challenging. In both, there will be an increase in proteinuria, hypertension and may be generalized symptoms as well as thrombocytopenia and renal impairment. In women with isolated preeclampsia, there should not be hematuria or urinary casts, falling complement or a rising dsDNA. However, of course, a flare of lupus nephritis increases the risk of preeclampsia so again distinguishing the two can be challenging, and the therapeutic pathways are different – preeclampsia mandates delivery sooner rather than later, lupus nephritis mandates immunosuppressive treatment. Not yet in routine practice, but likely to be exceptionally helpful, is the use of angiogenic and anti-angiogenic factor levels to determine if there is preeclampsia. The PROMISSE study showed that having soluble Flt1 (sFLT1) in the highest quartile between 12 to 15 weeks gestation conferred an odds ratio for an adverse pregnancy outcomes of 17.3 (95% CI, 3.5-84.8) vs. women with sFlt1 in the lowest quartile.[7] From 16-19/40 weeks of gestation, the combination of low placental growth factor (PlGF) and high sFlt1 strongly predicted adverse pregnancy outcomes. [19] Later in pregnancy falling PlGF predicts the onset of preeclampsia even in women with pre-existing CKD. [20]

***Treatment of a Lupus Nephritis Flare***

Once a diagnosis of lupus or lupus nephritis flare in pregnancy has been diagnosed, therapy needs to be started without delay. A severe flare of lupus nephritis in a young woman in early pregnancy should lead to a discussion about therapeutic abortion. Sometimes this might be the safest option as the lupus can be treated optimally without the constraints imposed by the pregnancy. However, many women prefer not to abort especially later in pregnancy or if it might the woman's only chance of pregnancy, then attempting to treat is the correct course. All women with lupus should be on hydroxychloroquine unless contraindicated, and this can be started in pregnancy. In general, the first line approach would be steroids – and pulses of high dose methyl prednisolone can be given for rapid effect and this should reduce the requirement for oral steroids. Oral prednisolone can be started at 0.5mg/kg/day with the aim to taper as rapidly as tolerated.[17] Lupus nephritis requires immunosuppressive treatment in addition to steroids. The traditional approach has been to add or to increase maintenance azathioprine, up to 2mg/kg/day. We have found the use of the calcineurin agent tacrolimus very helpful – it is steroid sparing, leads to rapid reduction in proteinuria due to off target effects on podocyte stabilization and is well tolerated. We reported treatment of 9 women, 6 on maintenance tacrolimus and 3 with acute lupus nephritis flares, all of whom had good pregnancy outcomes.[21] Steroids and tacrolimus both increase the risk of gestational diabetes (GDM), the combination particularly so, and women must be monitored carefully for the onset of GDM. Additionally, women with significant proteinuria should have prophylactic low molecular weight heparin to reduce the risk of venous thromboembolism.

In later pregnancy, MMF or cyclophosphamide can theoretically be used to treat severe lupus or lupus nephritis, but at some point the decision needs to be jointly made whether it is safer

to deliver a premature baby and treat the mother and baby separately. Anecdotally, intravenous gammaglobulin can be used to treat cytopenias and skin flares in pregnancy though the evidence base is lacking. Rituxmab is not recommended for treatment of lupus in pregnancy. It is an IgG antibody transported across the placenta with resultant significant levels found in the fetus. There have been 256 pregnancies reported to registries and cases reports in women with malignancies and autoimmune disease who have been exposed to rituximab pre conception and during pregnancy. Of these, there were 172 live births, and miscarriage in 23% and termination in 19%. Among the live births there was no increase seen in birth defects, but haematological abnormalities were seen in 11 children. [22,23] Exposure to rituximab in the 2nd or 3rd trimester leads to cord levels of rituximab at equal or higher levels than maternal levels. The babies are B cell deplete, but normalise within 3 to 6 months after birth in 8 children studied.[22] There are no data on infections in these children or responses to vaccines, nor the long-term effects of such early B cell perturbation. The recommendation from the manufacturer is to wait one year after rituximab before conception. Currently, our advice is to only use rituximab when no other options are available to control the mother's disease effectively and probably not at all after the first trimester. A recent publication highlights the evidence (or more commonly the lack of evidence) for best use of anti-rheumatic drugs before and during pregnancy. [23] Women taking azathioprine, hydroxychloroquine, cyclosporin and tacrolimus can safely breastfeed their babies, [9,24-26] and women taking these drugs should not be discouraged from breast-feeding. There are no safety data yet on MMF so breastfeeding is discouraged if MMF is required.

**Summary Statements**

In summary, women with lupus and prior lupus nephritis can have safe, successful pregnancies. The art is planning before pregnancy wherever possible, in order to identify

those at high risk and to ensure medications are safe for pregnancy. During pregnancy, women need to be treated as high risk, observed for flares and the onset of preeclampsia, and the fetus carefully monitored for growth and blood flow. Excellent, immaculate, collaborative care between obstetricians, nephrologists, rheumatologists and multidisciplinary staff is essential

**Table 1**

**Issues to discuss at pre-pregnancy planning for women and once pregnant**

| | **Pre Pregnancy** | **Once pregnant** |
|---|---|---|
| Fertility and contraception | • Refer early for fertility advice if concerns | • Advise contraception post partum |
| Disease activity | • Ensure quiescent nephritis – biopsy if necessary and treat to complete remission prior to conception | • Monitor for disease flares – proteinuria, hypertension, impaired function, falling complement levels, rising dsDNA |
| Pharmacological management | • Review all medication – advise what to stop, what to continue, what to add.<br>• Stop renin-angiotensin blockers and biopsy if proteinuria rises to >1g/day.<br>• Ensure on safe immunosuppressants – stop MMF / Cyclophosphamide/ Methotrexate at least 90 days pre-pregnancy. Optimise maintenance therapy – steroids / azathioprine / tacrolimus / cyclosporine A all fine to continue.<br>• All women should be on hydroxychloroquine.<br>• Folic acid pre conception. | • Ensure renin-angiotensin blockers stopped as soon as pregnant if not already stopped.<br>• Ensure on safe immunosuppressants. If flares, can increase steroids / azathioprine / add tacrolimus or cyclosporine<br>• Hypertension – control BP with pregnancy safe medications<br>• Add aspirin by 12 weeks to reduce risk of preeclampsia.<br>• Low Molecular weight heparin if heavy proteinuria / LACpositive with prior thromboses |
| Identify women at high risk of adverse pregnancy outcomes | • Lupus anticoagulant positive<br>• Hispanic or non-white<br>• On anti-hypertensive agents (ensure BP well controlled)<br>• Prior lupus nephritis<br>• Platelet count <100 x $10^9$ cells/l<br>• *Physicians global assessment score >1 | • As for non pregnant |
| Preeclampsia | • Discuss ~8% of women with nephritis develop. Risk increases if any of the above high risk factors present | • Treat as high risk and monitor for onset of preeclampsia.<br>• Regular fetal growth scans<br>• Not yet routine –sFlt1 levels and ratio of sFlt1 to PlGF may prove helpful |
| Delivery | • Advise if high risk that likely to deliver <37/40 and if very early may be increased risk of operative delivery. | • Timing based on evaluation of maternal and fetal well being.<br>• Nephritis flare not an indication to deliver per se |

*Promisse Study[7]

**Table 2**

**Outcomes of pregnancies in women with lupus**

| | **Promisse Study[7] (Prospective)** | | | **Moroni et al[11] – (Prospective)** | **Smyth et al [18] Systematic Review (Retrospective)** |
|---|---|---|---|---|---|
| | | **Low Risk** | **High Risk** | **Prior LN** | |
| | N=385 | N= 129 | N= 50 | N= 71 | N= 2751 |
| Adverse Pregnancy Outcomes | 19% | 7.8% | 58% *(often between 23-35 weeks)* | 38.4% | |
| Preeclampsia | | | | 8.4% | 7.6% |
| Miscarriage/Stillbirth | 4.0% | 3.9% | 22% | 8.2% | 19.6% |
| Neonatal death | 1% | | | 0% | 2.5% |
| Pre term | 9% | | | 30.1% | 34.9% |
| IUGR | 10% | | | 16.4% | 12.7% |
| Birth weight <2.5 kg | | | | 27.4% | |
| Birth weight <1.5 kg | | | | 5.4% | |
| Flare of lupus nephritis (as judged only by rise in proteinuria) | 2.3% | | | 19.7% | 25.6% |

LN is lupus nephritis and IUGR in intrauterine growth restriction

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